NICE National Institute for Health and Care Excellence

Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161)

Assessment Report

Commercial in Confidence stripped version for consultation

Produced by: School of Health and Related Research (ScHARR), University of Sheffield

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Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence.

Title: Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161).

Produced by ScHARR, The University of Sheffield

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Sarah Davis acted as Principal Investigator for this assessment. Marrissa Martyn-St James and Edward Goka undertook the clinical effectiveness systematic review. Fiona Campbell undertook data checking and contributed to the clinical effectiveness review. Sarah Davis, Andrew Rawdin and Susi Sadler undertook the health economic review and developed the Assessment Group model. Ruth Wong carried out the electronic searches. Jean Sanderson conducted the network meta-analyses. John Stevens wrote the methods of analysis/synthesis section of the protocol, coordinated the evidence synthesis, and reviewed and commented on the draft report. Matt Stevenson provided guidance on the design of the model and commented on the draft report. Mark Strong conducted the non-parametric regression on the model outputs. Professor Peter Selby (University of Manchester) and Dr Neil Gittoes (University of Birmingham) provided clinical advice and commented on the draft assessment report.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the nine departments that comprise the Faculty of Medicine, Dentistry and Health at the University of Sheffield.

ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE). ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Health Economics Research Unit and Health Services Research Unit, University of Aberdeen; Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, University of Warwick; the BMJ Technology Assessment Group (BMJ-TAG), BMJ Evidence Centre and Kleijnen Systematic Reviews Ltd.

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1. DEFINITION OF TERMS 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.

A&E	Accident and Emergency
AE	Adverse Event
ALN	Alendronate
BMD	Bone Mineral Density
BMI	Body Mass Index
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curves
CI	Confidence Interval
CG146	Clinical Guideline 146 - Osteoporosis: assessing the risk of fragility fracture
CrI	Credible Interval
DES	Discrete Event Simulation
DIC	Deviance Information Criterion
DSU	Decision Support Unit
DXA	Dual energy X-ray Absorptiometry
eMIT	Electronic market information tool
eod	Every Other Day
EQ-5D	EuroQol-5D health questionnaire
FEV	Forced expiratory volume in one second
FRAX	WHO Fracture Risk Assessment Tool
FN BMD	Femoral neck bone mineral density
GI	Gastrointestinal
GP	General Practitioner
GPRD	General practice research database
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HRT	Hormone replacement therapy
HSE	Health Survey for England
HTA	Health technology appraisal
i.v.	Intravenous
IBN	Ibandronate

INB	Incremental net benefit
ICER	Incremental Cost-Effectiveness Ratio
IU	International Units
LS BMD	Lumbar spine bone mineral density
mg	Milligram
MTA	Multiple Technology Appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-analysis
NNT	Number needed to treat
NSAIDS	Non-steroidal anti-inflammatory agents
NR	Not reported
ONS	Office of national statistics
PBO	Placebo
PM	Postmenopausal
PMO	Postmenopausal osteoporosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probability Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTH	Parathyroid hormone
QALY	Quality-Adjusted Life Year
QFracture	ClinRisk Ltd. algorithm to estimate risk of fracture
RCT	Randomised controlled trial
RIS	Risedronate
RR	Relative Risk
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TTO	Time trade-off
TH BMD	Total hip bone mineral density
WHO	World Health Organisation
ZOL	Zoledronate

2. EXECUTIVE SUMMARY

2.1 Background

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture. Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low energy') trauma. The World Health Organization (WHO) has quantified this as forces equivalent to a fall from a standing height or less. Whilst osteoporosis is an important predictor of the risk of fragility fracture, 70% of fragility fractures in postmenopausal women occur in those who do not meet the criteria for osteoporosis. The UK has one of the highest rates of fracture in Europe. Every year 300,000 people in the UK suffer a fragility fracture, including over 70,000 hip fractures.

2.2 Objectives

The key objectives of the assessment were:

- To evaluate the clinical effectiveness of each intervention
- To evaluate the adverse effect profile of each intervention
- To evaluate the incremental cost-effectiveness of each intervention compared (i) against each other and (ii) against non-active treatment
- To estimate the overall NHS budget impact in England

2.3 Methods

A systematic review of the literature including network meta-analyses (NMA) was conducted in order to evaluate the clinical effectiveness and safety of alendronate, ibandronate, risedronate and zoledronate in the prevention of fragility fractures. A review of the existing cost-effectiveness literature was undertaken. A *de novo* health economic model was constructed by the Assessment Group in order to evaluate the cost-effectiveness of the interventions under assessment.

2.4 Results

2.4.1 Number and quality of studies

A total of forty-six randomised controlled trials (RCTs) were identified that provided data for the clinical effectiveness systematic review. Alendronate was evaluated against placebo in seventeen RCTs. Daily oral ibandronate was evaluated against placebo in three RCTs and against i.v. administration in one RCT. Daily administration of oral ibandronate was

evaluated against monthly administration in one RCT. Risedronate was evaluated against placebo in twelve RCTs, and zoledronate was evaluated against placebo in four RCTs. One RCT evaluated alendronate compared with oral ibandronate, five RCTs evaluated alendronate compared with risedronate, one RCT evaluated zoledronate compared with alendronate, and one RCT evaluated zoledronate compared with risedronate.

The risk of bias associated with the included RCTs was assessed using the Cochrane risk of bias instrument. Attrition ≥10% across treatment groups was evident for 29 (63%) of the included RCTs. Five trials were reported as either open label or single blind and were considered at high risk of performance bias. Blinded outcome assessment was only reported by 13 (29%) trials.

2.4.2 Summary of benefits and risks

The outcome measures pre-specified in the final NICE scope were addressed by the included trial evidence to varying degrees. Femoral neck bone mineral density (BMD) was the most widely reported outcome. Fracture was the second most widely reported outcome. Adverse events were reported by the majority of included trials. Across the included trials there was limited reporting on the outcomes of compliance (adherence and persistence), hospitalisation and service use, and quality of life.

A total of 27 RCTs provided suitable fracture data for inclusion in the NMA and a total of 35 RCTs provided suitable femoral neck BMD data for inclusion in the BMD NMA. Based on the NMA, all treatments were associated with beneficial effects relative to placebo. For vertebral fractures and percentage change in BMD the treatment effects were also statistically significant at a conventional 5% significance level for all treatments. Pairwise comparisons between treatments indicated that no active treatments were statistically significantly more effective than other active treatments for fracture outcomes. For vertebral fractures and percentage change in BMD, the greatest effect was for zoledronate, though in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects.

Assessment of vertebral fractures within the trials was based on both clinical and morphometric fractures. Ideally, the effect of assessment method would have been assessed using meta-regression but there was insufficient data to facilitate this. Consideration of the trials reporting clinical fractures did not provide any evidence to suggest significantly different treatment effects according to assessment method.

Pooled RCT data for each bisphosphonate indicated no statistically significant differences in the incidence of upper gastrointestinal (GI) events, no evidence of significant differences in mortality, and no significant differences in participants withdrawing due to adverse events. Single RCT evidence indicated a statistically significant risk of upper GI events in men receiving risedronate compared with placebo, a statistically significant higher proportion of men and women dying following hip fracture who were receiving placebo compared with those receiving zoledronate, and a statistically significant higher proportion of men receiving alendronate withdrawing due to adverse events compared with placebo.

Pooled RCT data indicated evidence of influenza-like symptoms associated with zoledronate. Single RCT evidence indicated no statistically significant difference in the incidence of atrial fibrillation, incidence of bone pain or the incidence of stroke. Single RCT evidence indicated a statistically significant risk of eye inflammation in the first three days following administration of zoledronate. All RCTs evaluating zoledronate reported no cases of spontaneous osteonecrosis of the jaw.

Adverse events of hypocalcaemia and atypical femoral fracture were not reported outcomes by any RCT of any bisphosphonate.

2.4.3 Summary of cost-effectiveness evidence

The *de novo* economic model estimates that a strategy of no treatment is predicted to have the greatest net benefit for patients with an absolute risk <1.5% when using QFracture to estimate absolute risk and valuing a quality-adjusted life year (QALY) at £20,000. Alendronate is predicted to have the maximum incremental net benefit (INB) from 1.5% to 7.2% and risedronate is predicted to have the maximum INB from 7.2% upwards. However, the absolute costs and QALY gains are small in patients with low absolute risk and the probabilistic sensitivity analysis (PSA) suggested that there is considerable uncertainty regarding whether no treatment is the optimal strategy until the QFracture score is around 5.5% (the mean absolute risk for the 8th risk category for QFracture).

The mean INBs for oral bisphosphonate treatment compared with no treatment were positive across all FRAX risk categories. An exact threshold for the absolute risk at which the INB became positive was therefore not available but the minimum FRAX score in the modelled population was 1.2% and the lowest risk category (containing one 10th of the modelled population) had a mean absolute risk of 3.1%. Oral ibandronate is predicted to have the highest INB compared with no treatment up to 8.6%, with alendronate having the highest INB from 8.6% to 38.5% and risedronate having the maximum INB above 38.5%. The PSA

suggested that there was a low probability of the no treatment strategy being optimal across all FRAX risk categories when valuing a QALY at £20,000. However, the PSA also demonstrated that there is considerable uncertainty regarding the optimal bisphosphonate treatment with all of the oral bisphosphonates having reasonably similar probabilities of having maximum INB across most of the FRAX risk categories.

Contrastingly i.v. bisphosphonates were predicted to have lower INBs than oral bisphosphonates across all levels of absolute risk when estimated using either QFracture or FRAX. In the highest risk categories the incremental cost-effectiveness ratios (ICERs) for i.v. ibandronate and i.v. zoledronate compared with oral bisphosphonates were consistently over £50,000 per QALY even though the basecase analysis assumed longer durations of persistence for i.v. bisphosphonates than oral bisphosphonates. Although the mean INB compared with no treatment for i.v. ibandronate did become positive at very high levels of absolute risk when using QFracture, the results when using FRAX went in the opposite direction. This may be due to the few number of patients and parameter samples informing the estimates at high levels of absolute risk which makes these estimates more uncertain.

The results appeared to be broadly similar across the majority of the structural sensitivity analyses which examined the application of alternative data or assumptions. The results were more favourable to treatment when assuming full persistence with treatment for the intended treatment duration (3 years for zoledronate and 5 years for all other bisphosphonates) or when assuming no adverse events. The sensitivity analysis examining an adverse event rate of 30% in the month following initiation of oral bisphosphonate therapy showed that the cost-effectiveness of oral bisphosphonates is very sensitive to the rate of adverse events experienced. The INBs versus no treatment fell below zero (when valuing a QALY at £20,000) for all ten QFracture risk categories and for all but the highest FRAX risk category when assuming an adverse event rate of 30% in the first month of oral bisphosphonate treatment.

Two structural sensitivity analyses which varied the way in which the fracture risk was estimated showed results which were broadly similar for QFracture but slightly less favourable for FRAX. In these sensitivity analyses the cost-effectiveness estimates from the QFracture and FRAX model were closer together for patients with similar mean absolute risk than in the basecase.

2.5 Discussion

2.5.1 Strengths, limitations of the analyses and uncertainties

The clinical effectiveness systematic review was based on rigorous methods, with comprehensive searches for evidence, a good level of consistency between reviewers in study selection and double checking of data extraction. A formal assessment of methodological quality of included trial was undertaken. Attrition ≥10% across treatment groups was evident for 63% of the included RCTs.

Fracture data suitable for inclusion in the NMA were reported for 35 (27%) of the 46 included RCTs and femoral neck BMD data suitable for inclusion in the NMA were reported for 35 (76%). For fracture there was variability across the included trials in the skeletal fracture site evaluated, the most frequently evaluated being vertebral fracture. Femoral neck BMD summary statistics were not provided by all trials but were extracted from graphical representations where possible. Network meta-analyses were performed to permit a coherent comparison of the efficacy of interventions in terms of fracture and femoral neck BMD.

Adverse event data were widely reported, and supplemented by review evidence of observational data. Evidence for compliance and persistence was mainly limited to review evidence of observational data.

The Assessment Group's economic analysis has a number of strengths:

- The patient-level simulation approach used in the Assessment Group economic model allowed for the distribution of patient characteristics to differ across the risk categories providing estimates of cost-effectiveness that have taken into account the differing consequences of fracture in patients with different characteristics.
- The economic modelling approach used allowed intervention thresholds to be linked to absolute risk measured using the two risk assessment tools recommended in Clinical Guideline 146 (CG146: Osteoporosis; assessing the risk of fragility fracture),[11] as specified in the scope.
- Non-parametric regression was used to estimate the relationship between INB and absolute risk when averaging over both parameter uncertainty and the stochastic uncertainty associated with patient level simulations.
- The Assessment Group economic model was underpinned by a network meta-analysis across all drug options which provided a consistent framework for synthesising relevant efficacy data within a single network of evidence.

The Assessment Group economic model is also subject to a number of limitations:

- In order to provide a single intervention threshold for each treatment that could be applied across the whole population, we had to assume that all of the bisphosphonate treatment strategies were viable treatment options across all patients eligible for risk assessment within CG146. This would not be true if the licensed indications for each intervention were to be strictly applied. Furthermore, the studies included in the NMA which informed the economic evaluation are not strictly exchangeable because not all interventions are licensed in all patient populations.
- The cost-effectiveness of treatment in the lowest risk categories was particularly sensitive to the assumptions regarding the adverse effects of treatment due to the low absolute QALY gains and cost savings attributable to prevented fractures.
- The results of structural sensitivity analyses suggest that the model using FRAX to estimate absolute risk may have overestimated the INB of treatment compared with no treatment due to the method used to estimate time to fracture from absolute risk.

Key uncertainties in this assessment include:

- There was no evidence of differential treatment effects with respect to gender and age. However, there was some heterogeneity in treatment effects between studies suggesting differential treatment effects according to study characteristics and the effect of treatment on femoral neck BMD depended on the baseline response.
- It is uncertain whether the cost-effectiveness of bisphosphonate treatment at a particular level of absolute fracture risk would be similar for patients who have been assessed using the FRAX algorithm for patients with known BMD.
- The incidence of upper GI adverse events following initiation of oral bisphosphonate treatment is uncertain as the findings differ between the RCT evidence and the observational evidence from prescription event monitoring studies.

2.5.2 Generalisability of the findings

The majority of included trials typically excluded people with underlying conditions or receiving medications that affect bone metabolism. Furthermore, people with a history of or receiving medication for upper gastrointestinal tract disorders were also excluded by the majority of included trials. Therefore, the effects of alendronate, ibandronate, risedronate and zoledronate are unknown in these populations.

2.5 Conclusions

All treatments were associated with beneficial effects relative to placebo. For vertebral fractures and percentage change in BMD the treatment effects were also statistically significant for all treatments. For non-vertebral fractures the treatment effects were statistically significant at a conventional 5% level for risedronate, alendronate and zoledronate. For the outcomes of hip fracture and wrist fracture all treatments were associated with beneficial treatment effects relative to placebo, although the treatment effects were not statistically significant at a conventional 5% level. Pairwise comparisons between treatments indicated that no active treatment was significantly more effective than other active treatments for fracture outcomes. For vertebral fractures and percentage change in BMD, the greatest effect was for zoledronate, though in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects.

For the majority of adverse events reported in RCTs no significant difference was found between active treatment and placebo suggesting that bisphosphonates are generally well tolerated in patients enrolled within clinical trials. Prescription event monitoring study data suggests a high level of reporting of a number of conditions in the first month of therapy with alendronate or risedronate, particularly those affecting the upper gastrointestinal tract suggesting that oral bisphosphonates may be less well tolerated in clinical practice. A significant difference in the incidence of influenza-like symptoms was identified from the RCTs for zoledronate compared with placebo, although clinical advice was that these symptoms are generally limited to the first dose and usually last only a few days.

The *de novo* economic model estimates that when using QFracture to estimate absolute risk, a strategy of no treatment is predicted to have the greatest net benefit, when valuing a QALY at £20,000, in the lowest risk patients (QFracture absolute risk <1.5%), with oral bisphosphonates having the greatest INB at higher levels of absolute risk. However, the absolute costs and QALY gains are small in patients with low absolute risk and the PSA suggested that there is considerable uncertainty regarding whether no treatment is the optimal strategy until the QFracture score is around 5.5% (the mean absolute risk for the 8th risk category for QFracture).

The mean INBs compared with no treatment (when valuing a QALY at £20,000) were positive for all oral bisphosphonate treatments across all FRAX risk categories. However, in the basecase scenario the INBs of bisphosphonate treatments compared with no treatment were generally higher for FRAX than QFracture for risk categories with similar absolute

fracture risk. We would expect from the way the model is structured that the threshold for cost-effective treatment would be broadly similar across the two risk scores. The results of two structural sensitivity analyses suggest that the because analysis may have overestimated the fracture risk in the model based on FRAX due to the method used to estimate time to fracture from the FRAX absolute risk estimates. Given this possible bias in the estimates generated by the model using the FRAX absolute risk estimates, and our belief that the results should be broadly similar across the two risk scores, it would be reasonable to assume that the absolute risk thresholds estimated in the QFracture model could be applied to patients whose score had been calculated using either QFracture or FRAX.

The *de novo* economic model suggests that the cost-effectiveness of i.v. bisphosphonates is less favourable than for oral bisphosphonates with a negative INB (when valuing a QALY at £20,000) compared with no treatment estimated for both i.v. bisphosphonates across all ten risk categories for both FRAX and QFracture.

2.6.1. Implications for service provision

The prescribing of oral bisphosphonates in patients who have already received risk assessment under CG146 is not anticipated to have any major implications for service provision as these can be prescribed in primary care. If i.v. bisphosphonates were to be widely prescribed across the population eligible for risk assessment under CG 146, it is likely that additional capacity would be required in existing services to administer these treatment in secondary care.

3. BACKGROUND

3.1. Description of health problem

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (a broken bone resulting from a fall at standing height or less). An internationally accepted definition provided by the World Health Organization (1994) defines the condition as bone mineral density (BMD) 2.5 standard deviations (SDs) below peak bone mass (20-year-old healthy female average) as measured by DXA (dual energy X-ray absorptiometry).[2] The term "established osteoporosis" includes the presence of a fragility fracture.[2] Primary osteoporosis can occur in both men and women, but is most common in women after menopause when it is termed postmenopausal osteoporosis. In contrast, secondary osteoporosis may occur in anyone as a result of medications, specifically glucocorticoids, or in the presence of particular hormonal disorders and other chronic diseases.[3]

Osteoporosis was not classified as a disease until relatively recently.[4] Previously, it was considered an inevitable accompaniment of aging. During human growth, bone formation exceeds resorption.[5] Peak bone mass is achieved by men and women in the third decade of life.[6] There then follows a period during which there is a constant turnover of bone formation when the amount of bone formed by osteoclasts approximately equals the amount resorbed by osteoblasts.[6] Both men and women lose bone after midlife when bone resorption starts to exceed formation and in women there is also a significant rapid loss due to menopausal hypogonadism.[7,8]

In 2010, the number of postmenopausal women living with osteoporosis in the UK, based on the definition of a BMD at least 2.5 SDs lower than a young healthy women (T score≤-2.5 SD), was predicted to increase from 1.8 million in 2010 to 2.1 million in 2020 (+16.5%).[9] As a result, the prevalence of osteoporosis in the general population of women aged ≥50 years was assumed to remain stable over time, at approximately 15.5%. In 2014, osteoporosis prevalence in women has been reported to range from 9 % (UK) to 15 % (France and Germany) based on total hip BMD and from 16 % (USA) to 38 % (Japan) when spine BMD data were included. For males, prevalence ranged from 1 % (UK) to 4 % (Japan) based on total hip BMD and from 3 % (Canada) to 8 % (France, Germany, Italy, and Spain) when spine BMD data were included.[10]

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low energy') trauma. The World Health

Organization (WHO) has quantified this as forces equivalent to a fall from a standing height or less. Whilst osteoporosis is an important predictor of the risk of fragility fracture, 70% of fragility fractures in postmenopausal women occur in those who do not meet the criteria for osteoporosis.[11] The UK has one of the highest rates of fracture in Europe, every year 300,000 people in the UK suffer a fragility fracture, including over 70,000 hip fractures.[12]

3.2 Impact of health problem

3.2.1 Significance for patients

Fractures cause significant pain, disability and loss of independence and can be fatal.[13] Osteoporosis affects over three million people in the UK.[14] In the UK, 1,150 people die every month following a hip fracture.[15]

3.2.2 Significance for the NHS

In 2002 the cost to the National Health Service per annum was estimated to be £1.7 billion, with the potential to increase to £2.1 billion by 2020, as estimated in 2005.[16]

3.2.3 Measurement of disease

Quantitative diagnosis in the UK relies on the assessment of bone mineral density (BMD), usually by central dual energy X-ray absorptiometry (DXA). BMD at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to –2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of 1 or more fragility fractures.[17]

NICE Clinical Guideline 146 (CG146) recommends the use of absolute risk of fragility fracture and recommends the use of one of two assessment tools.[1] These tools are FRAX®[18] and QFracture®[19]. Both of these tools provide estimation of absolute fracture risk over a 10-year period. The age ranges are FRAX 40 to 90 years and QFracture 30 to 99 years. The guideline recommends that assessment is indicated for all females over 65 years and all males over 75 years.[20] Above the age limit of the tools, people should be considered to be at high risk. Females between 50 and 65 years and males between 50 and 75 years should be assessed if they have additional risk factors of: previous fragility fracture, current or frequent recent use of oral or systemic glucocorticoids, a known secondary cause of osteoporosis, a history of falls, a family history of hip fracture, low body mass index, smoking or weekly alcohol intake greater than 14 units for females and 21 units for males. Routine assessment of risk is not recommended for people under 50 years unless they have major risk factors. The guideline suggests that risk tools are likely to provide an underestimate of risk when a

previous fracture has been a vertebral fracture, the alcohol intake is very high, the person has secondary causes of osteoporosis, or the person is receiving high-dose oral or high-dose systemic glucocorticoid. The guideline recommends that fracture risk in people less than 40 years should be assessed using BMD and only in those with major risk factors such as history of multiple fragility fractures, major osteoporotic fracture, or current/recent use of high-dose oral or high-dose systemic glucocorticoid therapy.

3.3. Current service provision

3.3.1 Clinical Guidelines

Currently, related NICE guidance includes a clinical guideline for identifying women and men at risk of fracture and three technology appraisals of treatments for post-menopausal women only.

3.3.2 Current NICE Technology Appraisal Guidance

NICE technology appraisal guidance 160 (TA160: alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women),[21] recommends alendronate as first-line treatment for the primary prevention of fragility fractures in postmenopausal women with osteoporosis who have an increased fracture risk defined by age, T-score, and number of independent clinical risk factors for fracture, or indicators of low BMD. For women who cannot take alendronate, NICE technology appraisal guidance 160[21] and 204 (denosumab for the prevention of osteoporotic fractures in postmenopausal women),[22] recommends risedronate, etidronate, strontium ranelate, teriparatide or denosumab, at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[23]

NICE technology appraisal guidance 161 (TA161: secondary prevention, in women who have already sustained a fracture),[24] recommends alendronate for secondary prevention of fragility fractures in post-menopausal women with confirmed osteoporosis. For women who cannot take alendronate, NICE technology appraisal guidance 161[24] recommends risedronate, etidronate, raloxifene, strontium ranelate, and teriparatide at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[23]

NICE technology appraisal guidance 204[22] recommends denosumab as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for

administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.[23]

3.3.3. Current service cost

Hernlund *et al.* (2013)[25] reviewed the literature on fracture incidence and costs of fractures in the 27 European Union (EU) countries and incorporated data into a model estimating the clinical and economic burden of osteoporotic fractures in 2010. The cost of osteoporosis, including pharmacological intervention in the EU in 2010 was estimated at €37 billion. Costs of treating incident fractures represented 66% of this cost, pharmacological prevention represented 5% and long-term fracture care represented 29%. Excluding cost of pharmacological prevention, hip fractures represented 54% of the costs, vertebral and forearm fractures represented 5% and 1%, respectively; and "other fractures" represented 39 %. The estimated number of life-years lost in the EU due to incident fractures was approximately 26,300 in 2010. The total health burden, measured in terms of lost quality-adjusted life years (QALYs), was estimated at 1,180,000 QALYs for the EU.

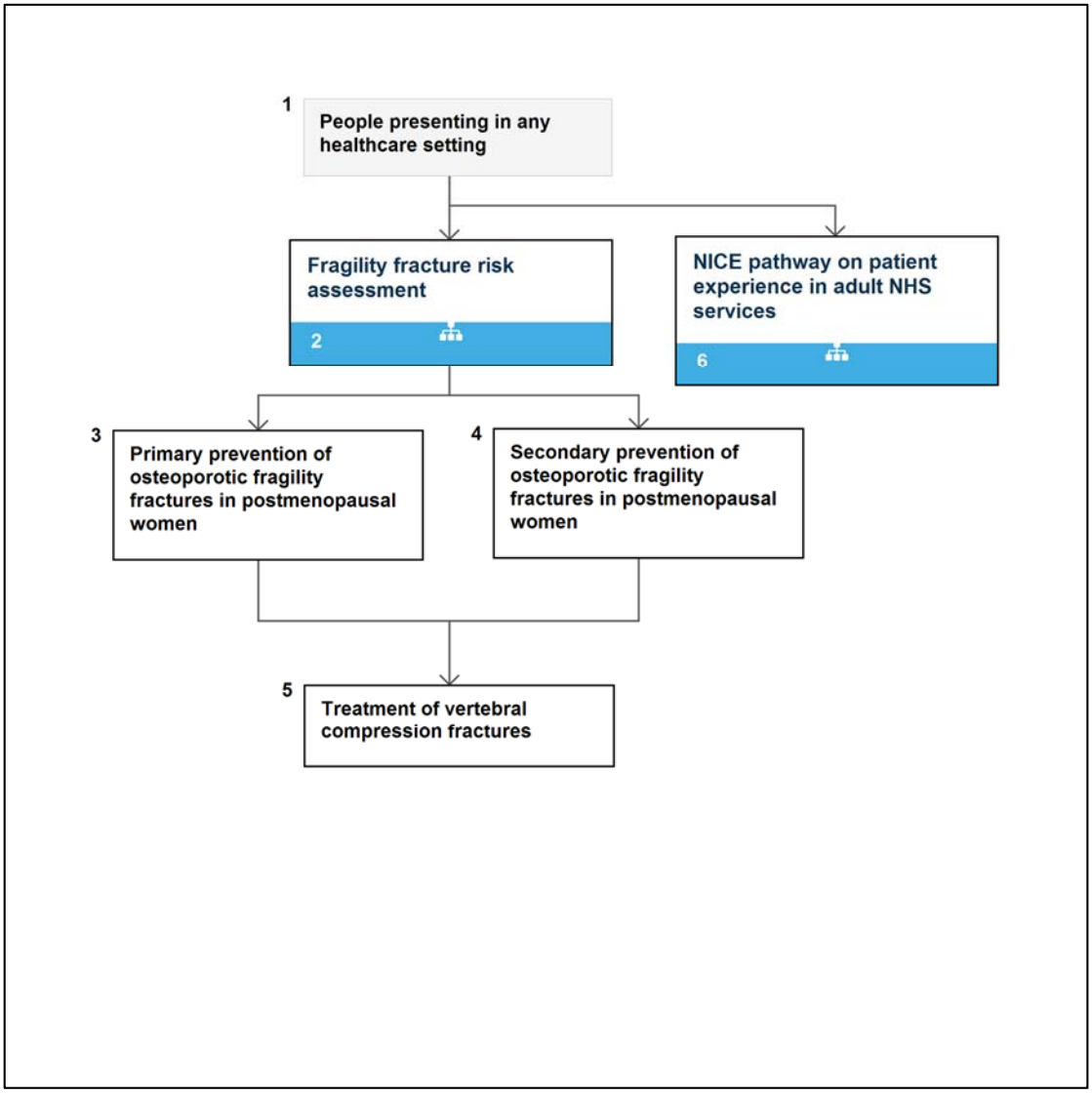
In the UK the cost of osteoporosis (excluding the value of QALYs lost) in 2010 was estimated by Hernlund *et al*.[26] at €103million (£88.3million in 2014 prices) for pharmacological fracture prevention, €3,977million (£3,410milion in 2014 prices) for cost of fractures, and €1,328million (£1,139million in 2014 prices) for cost of long-term disability. The 2010 cost of UK osteoporosis fracture in relation to population and healthcare spending was €5,408million (£4,637million in 2014 prices). It should be noted that the prices reported by Hernlund et al. in Euros have been converted back to £ sterling (2006 prices). The conversion ratio used by Hernlund et al. was estimated (at 1.4065) by comparing the unit cost for nursing home stay against the cited UK specific source data from 2006. They have then been uplifted to 2014 prices using the hospital and community health services (HCHS) inflation indices from the PPSRU[27] (290.5 for 2013/2014 versus 240.9 for 2005/2006).

3.3.4 Variation in services and uncertainty about best practice

3.3.5 Current treatment pathway

The NICE 2014 Osteoporosis overview pathway is presented in Figure 1.[28] This pathway covers NICE guidance on osteoporosis in adults (18 years and older), including assessing the risk of fragility fracture and drug treatment for the primary and secondary prevention of osteoporotic fragility fractures.

Figure 1: Osteoporosis overview pathway

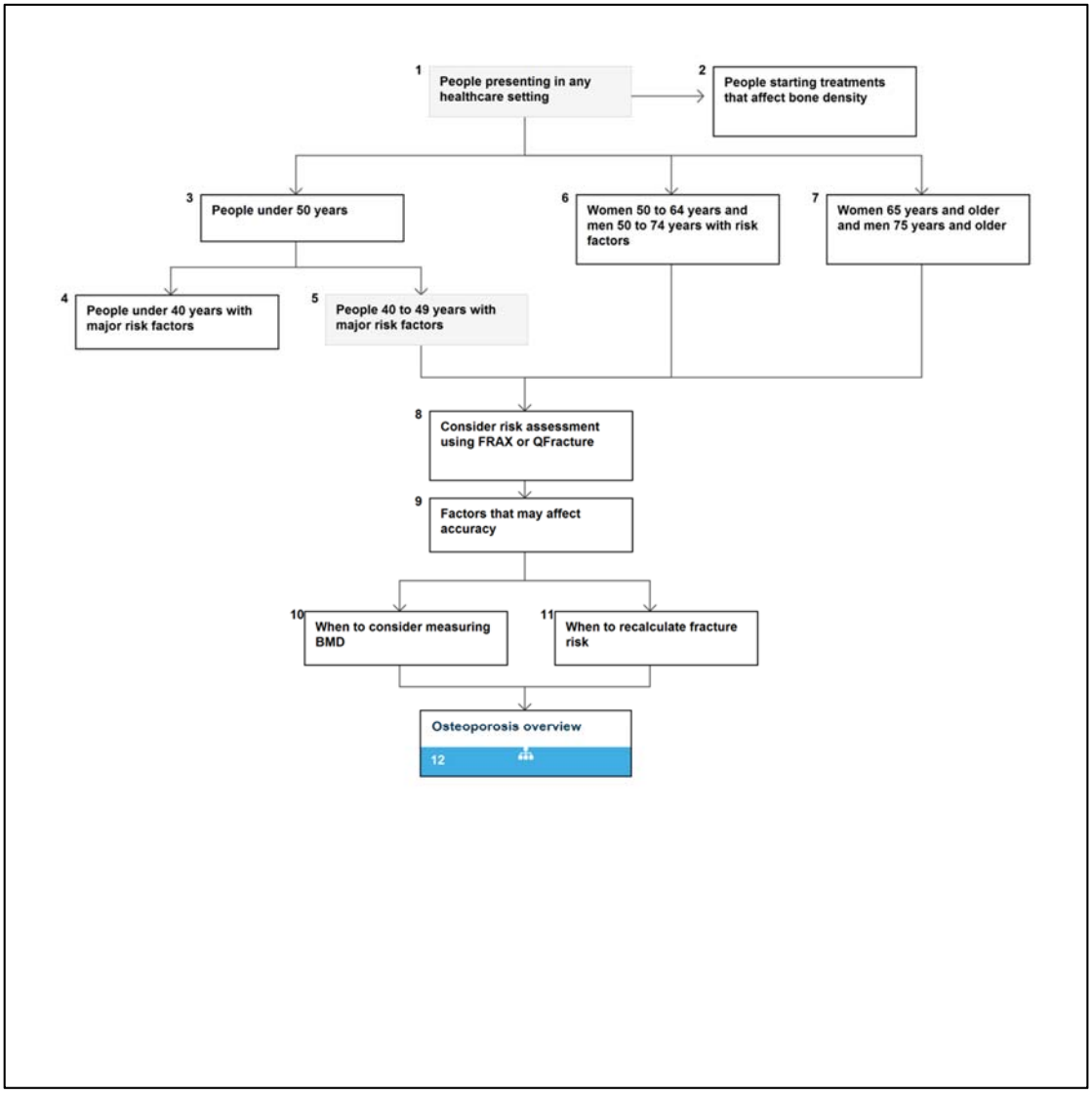


Source http://pathways.nice.org.uk/pathways/osteoporosis[28]

Current clinical guidelines recommend that fracture risk is assessed by estimating the absolute risk of fracture whereas technology appraisals use a defined set of risk factors to delineate people at risk. The modelling approach used in this assessment report allows intervention thresholds to be linked to absolute risk measured using the two risk assessment tools recommended in CG146[1] as specified in the scope.[23]

The NICE 2014 Fragility fracture risk assessment pathway is presented in Figure 2.[29] This pathway covers NICE guidance on osteoporosis in adults (18 years and older), including assessing the risk of fragility fracture and drug treatment for the primary and secondary prevention of osteoporotic fragility fractures.[30]

Figure 2: Fragility fracture risk assessment pathway



Source

http://pathways.nice.org.uk/pathways/osteoporosis#path=view%3A/pathways/osteoporosis/fragility-fracture-risk-assessment.xml&content=view-index[29]

3.4. Description of technology under assessment

3.4.1 Interventions considered in the scope of this report

Four interventions will be considered within this assessment: alendronate, ibandronate, risedronate and zoledronate which are nitrogen containing bisphosphonates.

3.4.2 Mode of action

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone. Aminobisphosphonate inhibits prenylation of proteins and leads to osteoclast apoptosis, reducing the rate of bone turnover.[31]

3.4.3 Marketing license and administration method

(1) Alendronate (Fosamax, Fosamax Once Weekly and Fosavance [co-formulation with colecalciferol], MSD) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once daily or weekly. The 10 mg daily dose has also has a UK marketing authorisation for treating osteoporosis in men and for preventing and treating glucocorticoid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy, orally once daily.[23]

Non-proprietary alendronate (AAH, Accord, Actavis, Alliance Healthcare, Almus, Apotex UK, Fannin UK, Focus, Generics UK, Kent, Mylan UK, Phoenix Healthcare Distribution, PLIVA, Ranbaxy, Rosemont, Somex, Sun, Teva UK, Waymade, Wockhardt and Zentiva) also has a UK marketing authorisation for the same indications.[23]

Alendronate in the treatment of postmenopausal osteoporosis is administered orally 10 mg daily or 70 mg once weekly. Treatment of osteoporosis in men is 10 mg daily. Prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy is 10 mg daily. Treatment is administered while sitting or standing and patients should remain seated or stood for at least 30 minutes.[32]

(2) Ibandronate (Boniva, Roche) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once monthly or every 3 months by intravenous injection. Non-proprietary ibandronate (Actavis UK, Consilient Health, Mylan UK, Sun and Teva UK) also has a UK marketing authorisation for the same indications[23].

Ibandronate in the treatment of postmenopausal osteoporosis is administered either by mouth 150 mg once a month or by intravenous injection over 15–30 seconds, 3 mg every 3 months. Oral treatment is administered while sitting or standing and patients should remain seated or stood for at least one hour.[32]

(3) Risedronate (Actonel and Actonel Once a Week, Warner Chilcott) has a UK marketing authorisation for treating postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, orally once daily or weekly. It has a marketing authorisation for preventing osteoporosis (including glucocorticoid-induced osteoporosis) in postmenopausal women, orally once daily, and for treating osteoporosis in men at high risk of fractures, orally once weekly. Non-proprietary risedronate (AAH, Actavis, Alliance Healthcare, Aspire, Aurobindo, Bluefish, Dr Reddy's Laboratories, Mylan UK, Phoenix Healthcare Distribution, Ranbaxy,

Sandoz, Sovereign Medical, Teva UK, and Zentiva) also has a UK marketing authorisation for the same indications[23].

Risedronate in the treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures is administered 5 mg daily or 35 mg once weekly. For the prevention of osteoporosis (including glucocorticoid-induced osteoporosis) in postmenopausal women, administration is 5 mg daily. Treatment of osteoporosis in men at high risk of fractures is 35 mg once weekly. Patients should remain seated or stood for at least one hour after administration.[32]

(4) Zoledronate (Aclasta, Novartis) has a UK marketing authorisation for treating postmenopausal osteoporosis and osteoporosis in men (including glucocorticoid-induced osteoporosis in postmenopausal women and men) by intravenous infusion once a year.

Zoledronate in the treatment of postmenopausal osteoporosis and osteoporosis in men (including glucocorticoid-induced osteoporosis in men and postmenopausal women) is administered by intravenous infusion, 5 mg over at least 15 minutes once a year. In patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair.[32] Non-proprietary zoledronate (SUN Pharmaceuticals, Dr Reddy's and Teva UK) also has a UK marketing authorisation for the same indications.[33]

3.4.4 Contraindications, special warnings and precautions

The SmPC for each intervention describes the contraindications and special warnings for bisphosphonates.[33-39]

(1) Alendronate 10mg daily and 70mg weekly tablet is contraindicated in: abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia, inability to stand or sit upright for at least 30 minutes, hypersensitivity to alendronic acid or to any of the excipient, and hypocalcaemia. Additional contraindications for the 70mg oral solution are patients who have difficulty swallowing liquids and patients at risk of aspiration.[34,35]

Special warnings and precautions for use include patients with active upper gastro-intestinal problems, and patients with known Barrett's oesophagus. Patients with signs or symptoms signalling a possible oesophageal reaction should be instructed to discontinue treatment. While on treatment, patients with concomitant risk factors for osteonecrosis of the jaw (e.g.,

cancer, chemotherapy, radiotherapy, glucocorticoids, poor oral hygiene, periodontal disease) should avoid invasive dental procedures if possible.[34,35]

(2) Ibandronate 150mg tablet is contraindicated in: hypersensitivity to ibandronic acid or to any of the excipients, hypocalcaemia, abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia, and inability to stand or sit upright for at least 60 minutes. The 3ml solution for injection every 3 months is contraindicated for patients with hypersensitivity to ibandronic acid or to any of the excipients and patients with hypocalcaemia.[36,37]

Special warnings and precautions for use include patients with existing hypocalcaemia and patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers) (oral administration). Intravenous administration may cause a transient decrease in serum calcium values. Adequate intake of calcium and vitamin D is important in all patients. Patients should be instructed to discontinue ibandronic acid and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain, or new or worsening heartburn. While on treatment, patients with concomitant risk factors for osteonecrosis of the jaw (e.g., cancer, chemotherapy, radiotherapy, glucocorticoids, poor oral hygiene, periodontal disease) should avoid invasive dental procedures if possible.[36,37]

(3) Risedronate 5mg daily and 35mg weekly tablet is contraindicated in: hypersensitivity to the active substance or to any of the excipients, hypocalcaemia, pregnancy and lactation, and severe renal impairment (creatinine clearance <30ml/min).[38,39]

Special warnings and precautions for use include patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia, patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet and patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus). Patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn. While on treatment, patients with concomitant risk factors for osteonecrosis of the jaw (e.g., cancer, chemotherapy, radiotherapy, glucocorticoids, poor oral hygiene, periodontal disease) should avoid invasive dental procedures if possible.[38,39]

(3) Zoledronic acid 5mg for infusion annually is contraindicated in: patients with hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients; patients with hypocalcaemia; patients with severe renal impairment with creatinine clearance < 35 ml/min; during pregnancy and breast-feeding.[33]

Special warnings and precautions for use include patients with severe renal impairment (creatinine clearance < 35 ml/min), patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after administration; and pre-existing hypocalcaemia. Adequate calcium and vitamin D intake are recommended. The incidence of post-dose symptoms occurring within the first three days after administration can be reduced with the administration of paracetamol or ibuprofen.[33]

The SmPCs for each intervention also refer to atypical subtrochanteric and diaphyseal femoral fractures being reported with bisphosphonate therapy and that during bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.[33-39]

3.4.5. Place in treatment pathway

Alendronate is recommended as first-line treatment for the primary prevention of fragility fractures in postmenopausal women with osteoporosis who have an increased fracture risk. Risedronate, raloxifene, strontium ranelate, and teriparatide are recommended for women at specified fracture risks who cannot take alendronate.

In addition to first-line treatment for the primary prevention of fragility fractures in postmenopausal women, alendronate is also recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis. Risedronate, raloxifene, strontium ranelate, and teriparatide are recommended for women at specified fracture risks who cannot take alendronate.[24]

Ibandronate and zoledronate do not have recommendations from NICE for the prevention of fragility fractures.

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either

risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.[22]

3.4.6 Identification of important subgroups

The final NICE scope specified subgroups based on patient characteristics that increase the risk of fracture (those specified in NICE Clinical Guideline 146[1]) or that effect the impact of fracture on lifetime costs and outcomes.[23]

3.4.7. Current usage in the NHS

None of the submissions contained evidence on the current usage of bisphosphonates within the NHS. Data from the 2013 Prescription Cost Analysis were analysed to determine the level of bisphosphonate usage within primary care across England in 2013.{Prescribing and Primary Care Team Health and Social Care Information Centre, 2014 1133490 /id} It can be seen from the data summarised in Table 1 that generic weekly alendronate was the most commonly prescribed preparation in primary care. Furthermore, generic prescriptions were more common than branded prescriptions across all treatments where generic prescriptions were reported. Unlike primary care, there is no central NHS collation of information on medicines issued and used in NHS hospitals. However, a 2012 report on hospital prescribing provides data on treatments recommended by NICE.{Prescribing Team Health and Social Care Information Centre, 2013 1133489 /id} From Table 4 of the report it can be seen that the vast majority of prescribing for alendronate and risedronate occurred in primary care with only 5% of the costs attributable to alendronate and risedronate prescribing occurring within secondary care. Advice from our clinical advisors suggests that the data in Table 1 may underestimate the prescribing of i.v. ibandronate and zoledronate which are usually prescribed in secondary care. Data on i.v. bisphosphonates are not reported in the data on hospital prescribing as data were only provided for individual drugs if they had already been recommended by NICE.

Table 1: Primary care prescribing of bisphosphonates per annum in 2013

Drug	Generic or branded	Dosing schedule	Prescriptions in thousands*	Description of preparations
Alendronate	Branded	Daily	0.749	Fosamax_Tab 10mg
		Weekly	25.655	Fosamax_Once Weekly Tab 70mg
	Generic	Daily	46.605	Alendronic Acid_Tab 10mg
		Weekly (tablet)	7,273.660	Alendronic Acid_Tab 70mg
		Weekly (liquid)	10.442	Alendronic Acid_Oral Soln 70mg/100ml S/F
Risedronate	Branded	Daily	1.023	Actonel_Tab 5mg
		Weekly	19.961	Actonel_Once a Week Tab 35mg
	Generic	Daily	25.777	Risedronate Sod_Tab 5mg
		Weekly	679.026	Risedronate Sod_Tab 35mg
Ibandronate	Branded	Monthly	22.670	Bonviva_Tab 150mg F/C
		Quarterly	0.181	Bonviva_Inj 3mg/3ml Pfs
	Generic	Monthly	204.006	Ibandronic Acid_Tab 150mg, Ibandronic Acid_Tab 50mg
		Quarterly	0.324	Ibandronic Acid_Inj 3mg/3ml Pfs
Zoledronate	Branded	Annually	0.070	Aclasta_I/V Inf 5mg/100ml Btl

* Prescription items dispensed in the community in 2013{Prescribing and Primary Care Team Health and Social Care Information Centre, 2014 1133490 /id}

3.4.8. Anticipated costs associated with interventions

Table 2 summarises the 2014 net costs associated with the interventions based on their list prices.[23] A list price was not available for generic zoledronate or i.v. ibandronate so the average prices reported in the electronic market information tool (eMIT) have also been included in Table 2.

Table 2: Acquisition costs associated with alendronate, ibandronate, risedronate, and zoledronate*

Drug	Unit type and dose	Price per unit
Alendronic acid (Non-proprietary)	Tablets, alendronic acid (as sodium alendronate) 10 mg	28-tab pack = £2.17*
Alendronic acid (Non-proprietary)	Tablets, alendronic acid (as sodium alendronate) 70 mg	4-tab pack = £1.01*
Alendronic acid (Non-proprietary)	Oral solution, sugar-free, alendronic acid (as sodium alendronate) 70 mg/100 mL	4 × 100-mL = £22.80*
Alendronic acid Fosamax® (MSD)	Tablets, alendronic acid (as sodium alendronate) 10 mg	28-tab pack = £23.12*
Fosamax® Once Weekly (MSD)	Tablets, alendronic acid (as sodium alendronate) 10 mg	4-tab pack = £22.80*
Ibandronic acid (Non-proprietary)	Tablets, ibandronic acid 50 mg	28-tab pack = £10.78*
Ibandronic acid Boniva® (Roche)	Tablets, f/c, ibandronic acid 150 mg	1-tab pack = £18.40*, 3-tab pack = £55.21*
Ibandronic acid Boniva® (Roche)	Injection, ibandronic acid 1 mg/mL	3-mL prefilled syringe = £68.64*
Ibandronic acid (Non-proprietor)	Injection, ibandronic acid 1 mg/mL	3-mL prefilled syringe = £19.38**
Risedronate Sodium (Non-proprietary)	Tablets, risedronate sodium 5 mg	28-tab pack = £13.24*
Risedronate Sodium (Non-proprietary)	Tablets, risedronate sodium 35 mg	4-tab pack = £1.18*
Risedronate Sodium Actonel® (Warner Chilcott)	Tablets, f/c, risedronate sodium 5 mg (yellow)	28-tab pack = £17.99*; 30 mg (white), 28-tab pack = £143.95*
Risedronate Sodium Actonel Once a Week® (Warner Chilcott)	Tablets, f/c, orange, risedronate sodium 35 mg	4-tab pack = £19.12*
Zoledronic acid Aclasta® (Novartis)	Intravenous infusion, zoledronic acid 50 micrograms/mL	100-mL bottle = £253.38*
Zoledronic acid (Non-proprietary)	Intravenous infusion, zoledronic acid 50 micrograms/mL	100-mL bottle = £94.67**

*Prices based on British National Formulary[32]

**Prices based on eMIT database[42]

4. DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

The aim of this assessment is to assess the clinical effectiveness and cost-effectiveness of alendronate, ibandronate, risedronate and zoledronate in the prevention of fragility fractures as compared against each other or a non-active treatment.

Interventions

Four interventions are considered within this assessment: alendronate, ibandronate, risedronate and zoledronate. These interventions are described in detail in Section 3.4.

Populations (including subgroups)

The assessment considers the following populations:

(1) All women aged 65 years and over and men aged 75 years and over.

(2) Women aged 64 years and under and men aged 74 years and under in the presence of risk factors, for example: previous fragility fracture; current use or frequent recent use of oral or systemic glucocorticoids; history of falls; family history of hip fracture; other causes of secondary osteoporosis; low body mass index (BMI) (less than 18.5 kg/m^2); smoking, alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

(3) Women aged 64 years and under and men aged 74 years and under with low BMD (a T-score of -1 SDs or more below the young adult mean).

An evaluation of the interventions in the following populations is outside of the appraisal scope and will not be considered in this assessment:

- Women aged 64 years and under without a risk factor (as listed under 4.5)
- Men aged 74 years and under without a risk factor (as listed under 4.5)

Relevant comparators

Bisphosphonates (alendronate, ibandronate, risedronate and zoledronate) may be compared against each other or a non-active agent, e.g., placebo.

Other bisphosphonates (e.g., etidronate) and other active agents (e.g., raloxifene, strontium ranelate, and teriparatide) will not be considered as comparators in this assessment.

Etidronate is not included as a comparator as it has been discontinued by the manufacturer in the UK. Non-bisphosphonates licensed for the prevention of fragility fractures in women and men will be considered in a separate Multiple Technology Appraisal (MTA).

Outcomes

The outcome measures to be considered included:

- fragility fracture (fractures that result from mechanical forces that would not ordinarily result in fracture)
    - hip fracture
    - vertebral fracture (where data allow clinical/symptomatic fractures will be reported separately from morphometric/radiographic fractures. Radiographic /morphometric fractures will be defined as those resulting in a 20% or greater reduction in vertebral height)
    - all non-vertebral fracture
    - wrist fracture
    - proximal humerus fracture
    - fragility fracture at other sites
- bone mineral density at the femoral neck assessed by DXA.
- mortality
    - all cause
    - mortality following hip fracture
    - mortality following vertebral fracture
    - mortality following fracture at site other than hip or vertebral
- adverse effects of treatment including but not limited to
    - upper gastrointestinal symptoms
    - osteonecrosis of the jaw
    - hypocalcaemia
    - bone pain (not associated with influenza-type symptoms)
    - atypical femoral fractures
    - influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors
    - conjunctivitis
    - atrial fibrillation

- stroke

- continuance and concordance (compliance)
- health-related quality of life
- healthcare resource use e.g., hospitalisation, entry into long-term residential care

Key issues

An evaluation of the interventions in the following populations is outside of the appraisal scope and will not be considered in this assessment:

- Women aged 64 years and under without a risk factor (as listed under 4.5)
- Men aged 74 years and under without a risk factor (as listed under 4.5)

4.2 Overall aims and objectives of assessment

This assessment addresses the question *"what is the clinical effectiveness and cost-effectiveness of alendronate, ibandronate, risedronate and zoledronate in the prevention of fragility fractures as compared against each other or a non-active treatment?"*

More specifically, the objectives of the assessment are to:

- evaluate the clinical effectiveness of each intervention
- evaluate the adverse effect profile of each intervention
- evaluate the incremental cost-effectiveness of each intervention compared against (i) each other and (ii) no active treatment
- estimate the overall NHS budget impact in England

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review of the literature with evidence synthesis including a network meta-analysis (NMA) was conducted in order to evaluate the clinical effectiveness and safety of alendronate, ibandronate, risedronate and zoledronate in the prevention of fragility fractures.

The systematic review of clinical effectiveness was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[43]

5.1 Methods for reviewing effectiveness

The protocol for this review is registered with PROSPERO (CRD42013006883)[44] and is presented in Appendix 1.

5.1.1 Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature relating to alendronate, ibandronate, risedronate and zoledronate within their licensed indications for the prevention of fragility fractures. The search strategy comprised the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1946 to Present
- Embase (Ovid) 1974 to 2014 September 23
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996-present
- Database of Abstract of Reviews of Effects (Wiley Interscience) 1995-present
- Cochrane Central Register of Controlled Trials (Wiley Interscience) 1898-present
- Health Technology Assessment Database (Wiley Interscience) 1995-present
- Cumulative Index to Nursing and Allied Health Literature (EBSCO) 1981 to present
- Science Citation Index Expanded (Web of Science) 1900-present
- Conference Proceedings Citation Index - Science (Web of Science) 1990-present
- BIOSIS (Web of Science) 1926-present

Existing evidence reviews,[20] commissioned by NICE, which included literature published up to June 2008, were assumed to have identified all papers relevant to this review published prior to 2008. Therefore searches were limited by date from 2008 until 26th September 2014. Searches were not restricted by language or publication type. Subject headings and keywords for 'osteoporosis' were combined with each of the named drug interventions. The MEDLINE search strategy is presented in Appendix 2. The search was adapted across the other databases. High sensitive study design filters were used to retrieve clinical trials and systematic reviews on MEDLINE and other databases, where appropriate. Industry submissions and relevant systematic reviews were also hand-searched in order to identify any further relevant clinical trials. Two clinical trials research registers (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform) were also searched for on-going and recently completed research projects. Citation searches of key included studies were also undertaken using the Web of Science database. All potentially relevant citations were downloaded to Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA) and deduplication of citation records undertaken.

5.1.2 Inclusion and exclusion criteria

Inclusion criteria have been defined in line with the final scope provided by NICE[23] and are outlined below.

5.1.2.1 Study selection process

The selection of eligible articles was undertaken by two reviewers (MMSJ and EG). Both reviewers sifted all downloaded citations (4,117). Citations not meeting the exclusion criteria based on the title and/or abstract were excluded at the sifting stage. All potentially relevant citations were marked to be obtained at full-text for further scrutiny. A check for consistency was undertaken using a Cohen's kappa coefficient of inter-rater agreement. A high level of agreement between reviewers (0.951) was observed. Any uncertainty regarding the eligibility of potentially relevant full text articles was resolved through discussion. Articles that were obtained as full-text for screening that were subsequently excluded were recorded together with the reason for exclusion. A table of excluded studies at full-text with reason is presented in Appendix 3.

5.1.2.2 Inclusion criteria

Studies were included in the review if they met the inclusion criteria outlined below.

a) Interventions

Any of the following interventions were included:

- Alendronate
- Ibandronate
- Risedronate
- Zoledronate

Studies in which the interventions were assessed in line with licensed indications were included in the systematic review. Studies that titrated doses upwards from unlicensed to licensed doses within treatment groups during the trial period were eligible for inclusion. Studies that evaluated both licensed and unlicensed dose study groups were included where outcome data for the licensed group only could be extracted. Data reported across licensed and unlicensed doses (pooled study groups) were not eligible for inclusion.

With respect to ibandronate, the license authorisation was supported by trials assessing the anti-fracture efficacy of 2.5mg per day and 20mg every other day compared with placebo (BONE[45,46]) and assessing non-inferiority of 2.5mg daily compared with 100mg or 150mg monthly on BMD (MOBILE[47,48]). A bridging study then demonstrating superiority for the current licensed intravenous dose of 3mg every three months compared with the 2.5mg once daily dose in terms of BMD (DIVA[49,50]). As such, these pivotal trials along with other trials comparing ibandronate 2.5mg with placebo were eligible for inclusion in addition to those assessing current licensed doses.

b) Populations

Studies were included that evaluated women aged 65 years and over or men aged 75 years and over. Studies were included that evaluated women aged 64 years and under and men aged 74 years and under in the presence of risk factors, for example: previous fragility fracture; current use or frequent recent use of oral or systemic glucocorticoids; history of falls; family history of hip fracture; other causes of secondary osteoporosis; low body mass index (BMI) (less than 18.5 kg/m^2); smoking, alcohol intake of more than 14 units per week for women and more than 21 units per week for men. Studies were also included that evaluated women aged 64 years and under and men aged 74 years and under with low BMD (a T-score of -1 SDs or more below the young adult mean). Studies that recruited mixed populations of men and women were also included, as were studies that recruited samples with mixed population characteristics, e.g., recruited a sample of women aged 65 and under with and without risk fractures.

In studies evaluating participants with risk factors for or the presence of secondary osteoporosis (e.g., treatment with aromatase inhibitors or androgen deprivation therapy) that did not evaluate a treatment of interest within its licensed indication, advice was sought from the clinical advisor (PS) regarding inclusion.

c) Comparators

Relevant comparators included: interventions compared with each other. Interventions could be compared with placebo or other non-active treatments (i.e., treatment without the potential to augment bone). Studies which administered calcium and / or vitamin D to patients in both the intervention and comparator arms were included (e.g. bisphosphonate plus calcium *vs.* placebo plus calcium).

d) Outcomes

Eligible outcomes for consideration included: fragility fractures, bone mineral density at the femoral neck, mortality, adverse effects, compliance, health-related quality of life, and healthcare resource use. These are described in full in section 4.1.

e) Study design

Randomised controlled trials (RCTs) were eligible for inclusion in the clinical effectiveness systematic review. If no RCTs were identified for an intervention, non-randomised studies were considered for inclusion. Non-randomised studies were also considered for inclusion, where necessary, as a source of additional evidence (e.g., relating to adverse events, long-term incidence of fragility fracture, etc.) associated with the interventions.

Studies published as abstracts or conference presentations were eligible for inclusion only if sufficient details were presented to allow an assessment of the trial methodology and results to be undertaken.

5.1.2.2 Exclusion criteria

The following types of studies were excluded from the review:

- Studies in patients with normal or unspecified BMD who have not been selected based on the presence of risk factors
- Studies in patients with other indications for bisphosphonate treatment e.g., Paget's disease, hypercalaemia of malignancy, metastatic breast cancer
- Studies where interventions are administered not in accordance with licensed indications

- Studies where interventions are co-administered with any other therapy with the potential to augment bone, unless concomitant treatments are specified in the summary of product characteristics
- Systematic reviews and clinical guidelines (these were used as sources of references)
- Studies which are considered methodologically unsound in terms of study design or the method used to assess outcomes
- Studies which are only published in languages other than English
- Studies based on animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as abstracts or conference presentations only, where insufficient details are reported to allow an assessment of study quality or results.

5.1.3 Data abstraction strategy

Data relevant to the decision problem were extracted by two reviewers (MMSJ or EG). Data were extracted without blinding to authors or journal. A data extraction form was developed and piloted on two included trials before use on all included trials. Data relating to study arms in which the intervention treatments were administered in line with their licensed indications were extracted; data relating to the unlicensed use of the interventions were not extracted. MMSJ and EG checked at least 10% of each other's data extraction forms. All extracted outcome data to be used in the analyses were double-checked by a third reviewer (FC). The safety data extracted were informed by the SmPCs for each product (available from http://www.medicines.org.uk/emc/).[33-39] The key safety issues included such items as the number of patients experiencing adverse events, number of patients withdrawing due to adverse events, number of patients experiencing upper GI tract symptoms, number of patients with osteonecrosis of the jaw, hypocalcaemia, bone pain, atypical femoral fractures, atrial fibrillation, or stroke; and the number of patients experiencing flu-like symptoms. Outcome data that were presented only in graphical format were digitised and estimated using xyExtract software version 5.1.[51] Where multiple publications of the same study were identified, data extraction was undertaken on all relevant associated publications, and findings were presented together with reference to their published source.

5.1.4 Critical appraisal strategy

The methodological quality of each included study was assessed by one reviewer (MMSJ or EG). The quality of included studies was assessed using the Cochrane Risk of Bias Tool.[52] This tool addresses specific domains, namely: sequence generation, allocation concealment,

blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. RCTs were classified as being at 'high risk' of attrition bias where drop-out in any treatment arm was ≥10%.[53] In order to inform the selective reporting domain of the Cochrane Risk of Bias tool a judgement was made that peer-reviewed articles which reported approval of a trial protocol or a trial registration number could be considered as being at 'low risk' of bias for this domain. All quality assessment findings were double checked by a second reviewer (MMSJ or EG).

5.1.5 Methods of data synthesis

The extracted data were presented for each study, both in structured tables and as a narrative description.

5.1.5.1 Methods for the estimation of efficacy using network meta-analysis

Network meta-analysis methods are described in full alongside results in Section 5.2.3.3.

5.1.5.2 Supplementary meta-analyses

Where considered appropriate, secondary outcomes of interest were analysed using classical meta-analysis methods. Meta-analysis was undertaken using Cochrane Review Manager software (version 5.2).[54] Outcomes reported as continuous data were summarised using a mean difference (MD) with 95% confidence intervals (95% CIs). Dichotomous outcomes were summarised as risk ratios (RRs) with associated 95% CIs. Where RCTs reported adverse events in sufficient detail, these were analysed as dichotomous data. Clinical heterogeneity across RCTs (the degree to which RCTs appear different in terms of participants, intervention type and duration and outcome type) was considered prior to data pooling. Random-effects models were applied. Effect estimates, estimated in Review Manager as Z-scores, were considered statistically significant at $p<0.05$.

5.2 Results

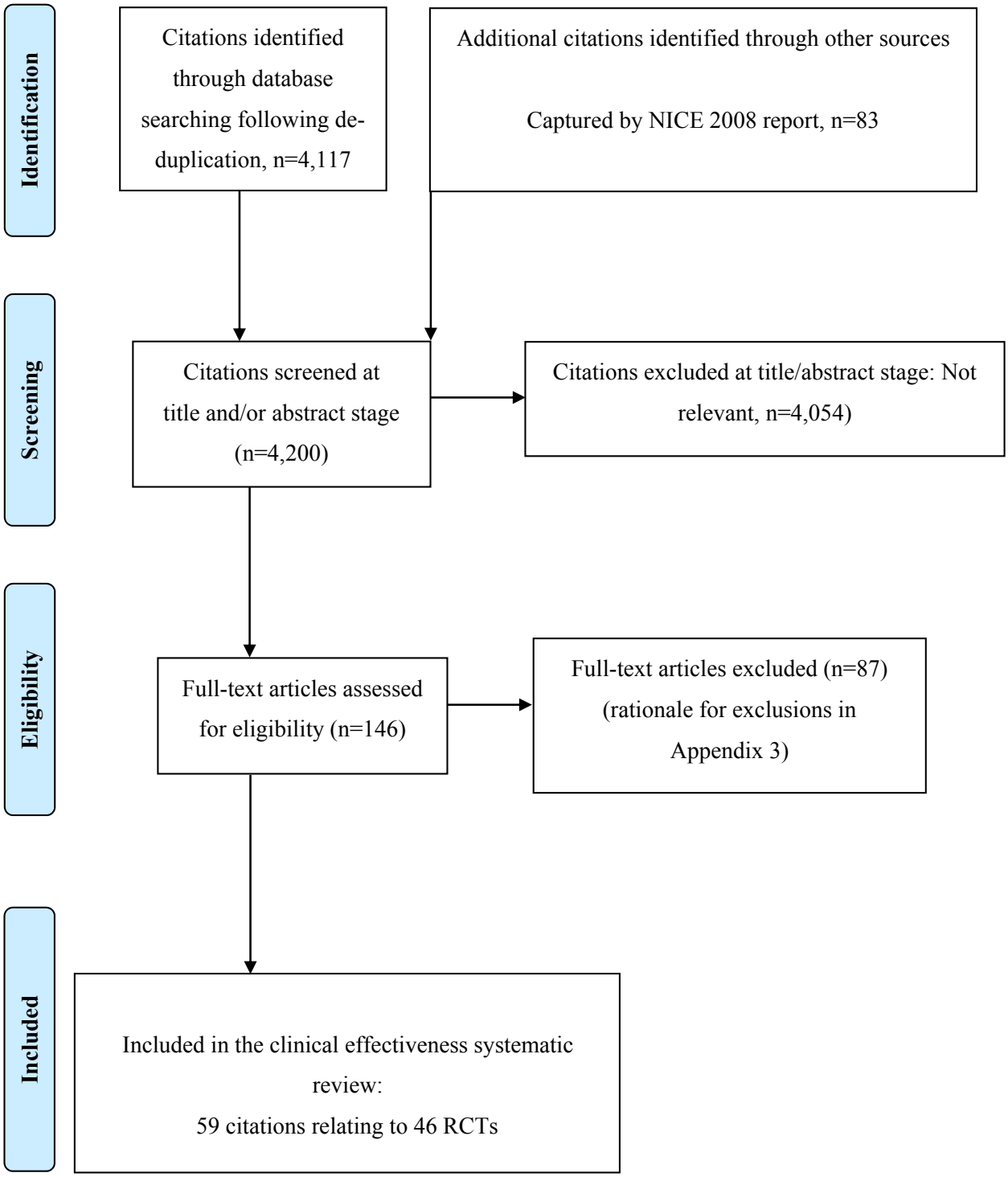
5.2.1 Quantity and quality of the available research

The searches described in Section 5.1.1 identified 4,117 potentially relevant citations from searches of electronic databases after removal of duplicates. A further 83 citations were identified from an existing evidence review commissioned by NICE.[20] Of these records, 4,054 were excluded at the title or abstract stage. Full texts of 146 citations were obtained for scrutiny. Of these, 87 citations were excluded (the Table of excluded studies with reason for exclusion is presented in Appendix 3). A total of 46 RCTs[45,47,49,55-97] reported across 589 citations were included in the review.

The search process is summarised in the form of a PRISMA flow diagram[98] in Figure 3.

The characteristics of the included RCTs are presented in Table 4.

Figure 3: Flow diagram of study selection process (adapted from PRISMA) – clinical effectiveness review



5.2.1.1 Study and population characteristics of included trials

A summary of the number of RCTs and citations by treatment along with the author, trial name (where reported) and population is presented in Table 3. The trial design of the included studies including country, inclusion/exclusion criteria, treatment doses and numbers randomised, outcome assessment methods and final follow-up are presented in Table 4. Characteristics of included participants including sex, age and baseline FN BMD and fractures are presented in Table 5.

Table 3: Summary of RCTs by treatment

Treatment, No. RCTs (n citations)	Trial and population
Alendronate vs. placebo 17 RCTs (19 citations)	Adami 1995 [55] Women with PMO Black 1996 [57] (FIT I) Women with PMO Cummings 1998 [66] (FIT II) Women with PMO Bone 2000 [59] Women with PMO Carfora 1998 [62] Women with PMO Chesnut 1995 [63] Women with PMO Dursun 2001 [67] Women with PMO Greenspan 2002 [69] Women with PMO Greenspan 2003 [70] Women aged 65 or older Ho 2005 [73] Women with PMO Klotz 2013[75] (CORAL) Men with androgen deprivation bone loss in non-metastatic prostate cancer Liberman 1995 [78] Seeman 1999 [99] Women with PMO Orwoll 2000[85] Men with OP Pols 1999[86] (FOSIT) Women with PMO Saag 1998 [93] (extension Adachi 2001 [100]) Men and women with Glucocorticoid-induced OP Shilbayeh 2004 [95] Women with PMO Smith 2004 [96] Men and women with asthma and/or chronic obstructive airways disease
Ibandronate vs. placebo Three RCTs (four citations)	Chesnut 2004[45]; Chesnut 2005 [46] (BONE) Women with PMO Lester 2008[76] (ARIBON) Postmenopausal women with breast cancer McClung 2009[82] Women with PMO
Ibandronate dose ranging trials Two RCTs (four citations)	Delmas 2006 [49] Eisman 2008 [50] (DIVA) Women with PMO Miller 2005[47] Reginster 2006 [48] (MOBILE) Women with PMO

Treatment, No. RCTs (n citations)	Trial and population
Risedronate vs. placebo 12 RCTs (15 citations)	Boonen 2009[60] Men with OP Choo 2011[64] Men with androgen deprivation bone loss in non-metastatic prostate cancer Cohen 1999 [65] Men and women (≥1y PM) aged 18-85 years old on glucocorticoids Fogelman 2000 [68] (BMD-MN) Women with PMO Hooper 2005 [74] Early PM women with OP Harris 1999 [72] (VERT-NA) (Extension Ste-Marie 2004[101]) Women with PMO Reginster 2000 [87] (VERT-MN) (Extension Sorensen 2003[102]) Women with PMO Leung 2005 [77] Women with PMO McClung 2001[80] Women with PMO Reid 2000 [88] Men and women taking glucocorticoids for ≥6 months. Ringe 2006[91] (Extension Ringe 2009 [103]) Men with OP Taxel 2010[97] Men aged >55 years and within a month of receiving an initial injection of ADT for prostate cancer
Zoledronate vs. placebo Four RCTs (six citations)	Black 2007[58] (HORIZON-PFT) Women with PMO (AEs following administration, Reid *et al.* 2010[104]) Lyles 2007[79] (HORIZON-RFT) Men and women 50 years of age or older within 90 days after surgical repair of a hip fracture (HRQoL, Adachi. 2011[105]) Boonen 2012[61] Men with OP McClung 2009 [81] Women with PMO
Alendronate vs. Ibandronate One RCT (one citation)	Miller 2008[83] (MOTION) Women with PMO
Alendronate vs. Risedronate Five RCTs (seven citations)	Atmaca 2006 [56] Women with PMO Muscoso 2004[84] Women with PMO Sarioglu 2006[94] Women with PMO Rosen 2005[92] (FACT) (Extension Bonnick 2005[106]) Women with PMO Reid 2006[89] (FACTS) (Extension Reid 2008[107]) Women with PMO.
Zoledronate vs. Alendronate One RCT (two citations)	Hadji 2010[108] Hadji 2012[71] (ROSE) Women with PMO
Zoledronate vs. Risedronate One RCT (one citation)	Reid 2009[90] (HORIZON) Men and women taking glucocorticoids ≥3mo and <3mo

HRQoL, Health-related quality of life; OP, osteoporosis; PMO, postmenopausal osteoporosis; ADT, androgen deprivation therapy

Table 4: Characteristics of included studies – clinical effectiveness review

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Alendronate vs. placebo					
Adami 1995[55] Italy Multicentre RCT, 11 centres Sponsor not reported	*Inclusion:* women at least 2 years past natural menopause; the majority were under 65 years. Each had lumbar spine bone mineral density (BMD) which was >2 SD below the mean for young. Evidence of previous vertebral fracture was not an entry criterion, and only 5% of subjects had prevalent fractures. *Exclusion:* evidence of any secondary cause of osteoporosis, other metabolic bone disease, hyper- or hypothyroidism. Medications affecting bone metabolism	PBO, n=71 ALN10mg/d, n=78 *Adjuvant:* Both groups, calcium 500mg/d	24 months BMD assessed at 24 months	*Primary:* change in LS lumbar spine BMD (L1-L4) *Secondary:* change in FN and trochanter spine BMD	*Fractures:* not an outcome *BMD:* DXA - (Hologic, Waltham, MA, USA; Lunar, Madison, WI, USA; Norland, WI, USA; and Sophos, Paris, France)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Black 1996 [57] (FIT I) USA Multicentre RCT, 11 centres Merck Research Labs.	*Inclusion:* Women aged between 55 and 81 years, postmenopausal for at least 2 years, had at least one vertebral fracture and FN BMD of 0.68 g/cm2 or less (≤2 SDs below normal young adult) *Exclusion:* Peptic-ulcer disease, dyspepsia requiring treatment, abnormal renal function, major medical problems that would preclude participation, severe malabsorption syndrome, hypertension, myocardial infarction, unstable angina, disturbed thyroid or parathyroid function, use of oestrogen, calcitonin, bisphosphonates or sodium fluoride.	PBO, n=1005 ALN10mg/d, n=1022 *Adjuvant:* Both groups, women with low calcium intake 500 mg/d calcium supplements and 250 IU/d vitamin D	36 months Lateral radiographs were obtained at baseline and at 24 months and 36 months	*Primary:* New vertebral fractures at 3 years - a new vertebral fracture if any of the ratios of vertebral heights was more than 3 SDs below the mean population norm for that vertebral level. *Secondary:* non-vertebral fractures (hip, wrist, and others); FN, LS and total hip BMD. Adverse events.	*Fractures:* Vertebrae were judged to be fractured by morphometric assessment using a translucent digitiser. Clinical fractures (non-spine clinical fractures, hip fractures, wrist fractures, and clinical vertebral fractures; and other clinical fractures) were reported by participants and confirmed by a required written report of a radiological procedure. *BMD:* DXA - QDR-2000 Hologic (Waltham, MA, USA)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Cummings 1998 [66] (FIT II) USA Multicentre RCT, 11 centres Merck Research Labs.	*Inclusion:* Women aged 55-80 years; postmenopausal for at least 2 years; FN BMD of 0.68 g/cm2 or less (≤2 SDs below normal young adult) *Exclusion:* Peptic-ulcer disease, dyspepsia requiring treatment, abnormal renal function, major medical problems that would preclude participation, severe malabsorption syndrome, hypertension, myocardial infarction, unstable angina, disturbed thyroid or parathyroid function, use of oestrogen, calcitonin, bisphosphonates or sodium fluoride.	PBO, n=2218 ALN10mg/d, n=2214 *Adjuvant:* Both groups, women with low calcium intake 500 mg/d calcium supplements and 250 IU/d vitamin D	48 months Lateral radiographs were obtained at baseline and at baseline and 48 months	*Primary:* Clinical fractures (vertebral and non-vertebral) confirmed by radiographs at 4.2 years. *Secondary:* Change in BMD of the hip and posterior-anterior spine and whole body; adverse events, from baseline in each group.	*Fractures:* Clinical fractures were defined as one diagnosed by a physician. Self-reports of fractures were confirmed by radiographic or other tests (not described). Traumatic fractures and fractures of the face/skull were excluded. Vertebral fractures were assessed by radiographs. Fracture was defined as 20% decrease in height and 4mm decrease in vertebral height *BMD:* DXA - QDR-2000 Hologic (Waltham, MA, USA)
Bone 2000[59] Countries not specified RCT, number centres not specified Merck Research Labs.	*Inclusion:* Postmenopausal osteoporotic women 42-82 years old, with hysterectomy; BMD<0.862g/cm2 on at least 3 vertebra, LS T score (SD) ≤-2.5 *Exclusion:* Metabolic bone disease, low vitamin D, oestrogen replacement therapy > 6mo, drugs that affect bone turnover, renal insufficiency, cardiac disease, upper GI disease	PBO, n=50 ALN10mg/d, n=92 *Adjuvant:* Both groups, 1000 mg/d calcium	24 months BMD assessed at 3, 6, 12, 18 and 24 months	*Primary:* Change BMD of the LS, at 24 months. *Secondary:* Change BMD of the total hip, FN, trochanter, and total body; biochemical markers of bone turnover; fractures; adverse events.	*Fractures:* Clinical fractures recorded as adverse events (assessment method not reported) *BMD:* Hologic QDR densitometers (QDR-1000, -1000/W, -1500 or -2000; Hologic, Waltham, MA)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Carfora 1998 [62] Italy Single centre RCT Sponsor not reported	*Inclusion:* Postmenopausal women (for at least 5 years); age 44 to 80; at least 2.5 SD below the mean value in premenopausal white women. *Exclusion:* Women with other causes of Osteoporosis or vitamin D deficiency, Paget's disease, hyperparathyroidism, peptic ulcer, abnormal renal/hepatic function, abnormalities of LS	PBO, n=34 ALN10mg/d, n=34 *Adjuvant:* Both groups, 500mg/d calcium	30 months BMD assessed every 5 months, X-rays at baseline and end treatment	*Primary:* Change BMD of the spine at 2.5 years. *Secondary:* Fractures; biochemical markers of bone turnover; and adverse events.	*Fractures:* X-rays of the thoracic and lumbar spine to evaluate fractures. No further details reported. *BMD:* DXA – Hologic QD|R1000
Chesnut 1995 [63] USA Multicentre RCT, 7 centres Merck Research Labs	*Inclusion:* women aged 42 to 75 years, at least 5 years postmenopausal, with lumbar spine BMD ≤0.88 g/cm" (approximately 2 SDs below young, normal US white female mean BMD values) *Exclusion:* medications affecting bone metabolism were excluded, the presence of spine or hip fractures attributable to osteoporosis.	PBO, n=31 ALN10mg, n=30 Also evaluated ALN5mg/d, n=32; 20mg, n=32; 40mg/PBO, n=32, 40/2.5mg, n=31 *Adjuvant:* Both groups, 500mg/d calcium	24 months BMD assessed every 3 months	*Primary:* change in BMD at LS, FN, TH, intertrochanter, Ward's triangle and the forearm, bine markers, adverse events *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA Hologic 1000w, Inc., Waltham, Massachusetts).

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Dursun 2001 [67] Turkey Single centre RCT Sponsor not reported	*Inclusion:* Postmenopausal women with BMD of 2 SD or more below young adult mean at either LS or FN *Exclusion:* History of drug /alcohol abuse, metabolic bone disease, GI/liver disease, renal failure/calculi, glucocorticoid therapy, malignancy, disorder of calcium metabolism and LS abnormalities preventing BMD evaluation.	Calcium 1000mg/d, n=50 ALN10mg + Ca 1000mg/d, n=51 Also evaluated calcitonin, n=50	12 months BMD and X-ray assessment at 6 and 12 months	*Primary:* Change of LS, FN, trochanter and ward's triangle BMD in each group at 12 months. *Secondary:* Number of factures; quality of life and pain; fractures; adverse events.	*Fractures:* X-rays of thoracic and lumbar vertebrae. A new vertebral fracture was defined as a decrease of 20% and at least 4mm in any vertebral height. *BMD:* DXA – model and manufacturer not reported
Greenspan 2002 [69] USA Multicentre RCT, 25 centres Merck Research Labs.	*Inclusion:* Ambulatory women in long-term care ≥65 years, LS or total hip BMD T-score ≤-2.0 SD *Exclusion:* Disorders of bone mineralisation; low vitamin D; hyperthyroidism; GI disease; use of bone-active agents.	PBO, n=164 ALN10mg/day, n=163 *Adjuvant:* Both groups, 1000 mg/d calcium and 400 IU/d vitamin D supplements.	24 months BMD assessed at 6, 12, 18 and 24 months	*Primary:* Change BMD of the LS, FN, hip and hip trochanter; and biochemical markers of bone turnover, at 2 years. *Secondary:* Adverse events including fractures.	*Fractures:* Clinical fractures recorded as adverse events (assessment method not reported) *BMD:* DXA - Hologic (Waltham, Mass.)
Greenspan 2003 [70] USA Single centre RCT NIH grant NR	*Inclusion:* Community-dwelling women aged 65 or older *Exclusion:* FN BMD ≥0.9 g/cm2 (=0 SD of mean peak). Disease or drugs affecting bone metabolism.	PBO, n=93 ALN10mg/d, n=93 *Adjuvant:* Women with low calcium intake, calcium 600 mg/d 200 IU/d vitamin D Both groups, vitamin D 400 to 800 IU/d	36 months BMD assessed at 6, 12, 18, 24 and 36 months	*Primary:* Change of BMD of the hip, spine, FN, trochanter, and ultradistal radius *Secondary:* Fractures and adverse events.	*Fractures:* Fracture reduction was not a primary end point – recorded as adverse events (assessment method not reported) *BMD:* DXA - QDR4500A Hologic (Bedford, Mass)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Ho 2005 [73] China RCT, number centres not reported MSD Ltd OP	*Inclusion:* Women with osteoporosis aged <75 years, postmenopausal for >3 years, and lumbar spine BMD -2.5 SDs below local peak age. *Exclusion:* Treatment with bisphosphonates of fluorides, SERMs or oestrogen, calcitonin or any other drug that could affect bone metabolism	Calcium 500mg/d, n=29 ALN10mg + Ca 500mg/d, n=29 *Adjuvant:* calcium 500 mg/d	12 months BMD assessed at 3, 6 and 12 months	*Primary:* Change in BMD at LS, FN and TH; bone markers; adverse events *Secondary:* not reported	*Fractures:* Fracture not an outcome *BMD:*DXA Hologic QDR
Klotz 2013[75] (CORAL) Canada. Multicentre RCT, 30 centres Abbot Laboratories	*Inclusion:* Men with histologically confirmed prostate cancer in whom ≥1 yr. of ADT was indicated *Exclusion:* Hypocalcaemia, abnormal renal/liver function, metabolic bone disease, bilateral hip replacement, prior treatment with bisphosphonates or therapy with glucocorticoids	PBO, n=102 ALN70/w, n=84 *Adjuvant:* Both groups, calcium 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* Change in LS BMD. *Secondary:* change in total hip BMD; changes in bone markers	*Fractures:* not an outcome *BMD:* DXA – model not reported

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Liberman 1995[78] One multicentre study was conducted in the United States, and the other in Australia, Canada, Europe, Israel, Mexico, New Zealand, and South America Phase III multicentre RCT Merck Research Labs.	*Inclusion:* Postmenopausal women (for at least 5 years); age 45 to 80; with LS BMD at least 2.5 SD below the mean value of in premenopausal white women *Exclusion:* Other disorders of BMD, abnormal hepatic function, abnormality of lumbar spine precluding assess of BMD, history of hip fracture, and prior bisphosphonates treatment within 12 months.	PBO, n=397 ALN5,10,20mg, n=526 *Adjuvant:* Both groups, 500mg/d calcium	36 months BMD and lateral spine films assessed at 12, 24 and 36 months	*Primary:* New vertebral and non-vertebral fractures; Change of BMD of the LS, FN, trochanter, and total body, in each group at 3 years. *Secondary:* Adverse events.	*Fractures:* The occurrence of new vertebral fractures and the progression of vertebral deformities were determined by an analysis of digitized radiographs, and loss of height was determined by sequential height measurements *BMD:* DXA - Hologic QDR-1000 or 1000/W (Hologic, Waltham, Mass.), Lunar DPX-L (Lunar, Madison, Wis.), or Norland XR-26 (Norland, Fort Atkinson, Wis.)
Orwoll 2000 [85] USA and 10 other countries Multicentre RCT, 20 centres Merck Research Labs.	*Inclusion:* Men with BMD at FN <2 SD below the mean value in normal young men and BMD at the LS <1 SD below the mean or a BMD of at least 1 SD below the mean at the FN and at least 1 vertebral deformity or a history of osteoporotic fracture. *Exclusion:* Secondary causes of osteoporosis, other bone diseases, vitamin D deficiency, renal disease, cardiac disease, cancer, peptic ulcer/oesophageal disease	PBO, n=95 ALN10mg/d, n=146 *Adjuvant:* Both groups, 1000 mg/d calcium and 400 IU/d vitamin D	24 months BMD assessed at 6, 12, 18 and 24 months X-rays at 24 months	*Primary:* Changes in BMD of the LS (L1-L4), FN, hip, and total body, between treatment groups, at 2 years. *Secondary:* Incidence of vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* To detect both vertebral fractures, X-ray films were assessed. both semiquantitative and quantitative morphometric methods were used. Non-vertebral (any site) from patient reporting confirmed by X-ray *BMD:* DXA - Hologic, (Waltham, Mass.), or Lunar, (Madison, Wis.)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Pols 1999 [86] (FOSIT) Europe, Latin America, Australia, Canada, South Africa, China Multicentre RCT, 153 centres Merck Research Labs.	*Inclusion:* Women ≤85 years old postmenopausal for ≥ 3yrs with LS BMD ≥ 2SD below mean for postmenopausal woman 20% to 50% above ideal weight. *Exclusion:* Metabolic bone disease, disturbed parathyroid/thyroid function, GI disease, myocardial infarction, hypertension/angina, organ disease; treatment with bisphosphonates, fluoride, vitamin A, vitamin D	PBO, n=958 ALN10mg/d, n=950 *Adjuvant:* Both groups, 1000 mg/d calcium.	12 months BMD assessed 3, 6 and 12 months	*Primary:* Change in BMD of the LS (L1-L4), FN, trochanter, and total hip, between treatment groups, at 1 year. *Secondary:* Incidence of vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* The occurrence of clinical fractures was captured through adverse event reporting. documentation for each fracture consisting of radiographs and/or radiology reports, hospital discharge reports with clinical diagnosis and/or confirmation by the investigator/treating physician was sought after completion of the study *BMD:* Hologic QDR densitometers (QDR-1000, -1000/W, -1500 or -2000; Hologic, Waltham, MA) or Lunar DPX densitometers (DPX, DPX-L or DPX-a; Lunar, Madison, WI),

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Saag 1998 [93] USA and 15 other countries. Multicentre RCT, 15 centres in the USA, and 22 in other countries. Merck & Co.	*Inclusion:* Men and women, 17 to 83 years of age, with underlying diseases requiring long-term oral glucocorticoid therapy at a daily dose of at least 7.5 mg of prednisone or its equivalent irrespective of baseline BMD *Exclusion:* Metabolic bone disease, a low serum vitamin D, concomitant therapy with drugs that affect bone turnover, pregnancy or lactation, renal insufficiency , severe cardiac disease, and a history of recent major upper GI disease.	PBO, n=159 ALN10mg/d, n=157 Also evaluated ALN5mg/d, n=161 *Adjuvant:* All groups, calcium 800-1000 mg/d and vitamin D 250-500IU/d	48 weeks BMD assessed at 4, 12, 24, 36 and 48 weeks, X-ray at 48 weeks	*Primary:* Change in LS BMD, from base line to week 48 between the groups. *Secondary:* Changes in BMD at FN, trochanter and total body; biochemical markers of bone turnover; and the incidence of new vertebral fractures.	*Fractures:* Radiographs of the lateral lumbar and thoracic spine - semi quantitative visual assessment: grade 0, normal; grade 1, 20-25% reduction in height, 10-20% area; grade 2, 25-40% reduction in height, 20 -40% area; grade 3, ≥40% reduction in height and area. Vertebral fractures with grades of 2 or higher were defined as prevalent fractures, and fractures that increased in severity by at least one grade were defined as incident fractures. *BMD:* DXA - Hologic (Waltham, Mass.) or Lunar (Madison, Wis.)
Adachi 2001[100] (Saag 1998 extension)	Patients continued to receive the double-blind study medication to which they had been randomized at the beginning of year 1	PBO, n=61 ALN10mg/d, n=55	24 months	*Primary:* Change in LS, from base line to week 48 between the groups. *Secondary:* Changes in BMD of the hip, FN, trochanter and total body; biochemical markers of bone turnover; and the incidence of new vertebral fractures.	

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Shilbayeh 2004 [95] Jordan RCT, number centres not reported Sponsor not reported	*Inclusion:* Menopausal or early menopausal women with osteoporosis - BMD ≥ 2.5 SD below the young adult mean *Exclusion:* not reported	PBO, n=27 ALN10mg/d, n=36 *Adjuvant:* Both groups, calcium 500mg/d and Vitamin D 0.25 mcg/d	12 months BMD assessed at 12 months	*Primary:* change in BMD at the LS and FN; adverse events *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA - Lunar DPXL densitometer (Lunar, Madison, WI).
Smith 2004 [96] Australia Multicentre RCT, 3 centres Merck, Sharp and Dohme	*Inclusion:* Patients with asthma and/or chronic obstructive airways disease with following risk factors: >2 courses of prednisolone in the last two years, forced expiratory volume in one second (FEV) < 50% predicted, any respiratory admission in the last five years, severely limited exercise tolerance (unable to walk > 100 m unaided), being a woman aged over 50 and sustaining a bone fracture after the age of 40 *Exclusion:* known renal disease or symptoms of dysphagia, dyspepsia, use of proton pump inhibitors or alcohol dependence) or history of bilateral hip replacements.	PBO, n=79 ALN10mg/d, n=66 *Adjuvant:* Both groups, calcium 600 mg/d	12 months BMD assessed at 12 months	*Primary:* change in BMD at the LS and FN and whole femur *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA - Lunar (Lunar, Madison, WI).

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Ibandronate vs. placebo					
Chesnut 2004[45]; Chesnut 2005 [46] (BONE) Europe and North America Multicentre RCT, 73 centres Hoffman-La Roche Ltd	*Inclusion:* patients, aged 55-80 years, ≥5 years post menopause, with one to four prevalent vertebral fractures (T4-L4), and with a BMD T-score of -2.0 to -5.0 in at least one vertebra (L1-L4) *Exclusion:* upper GI disorders, LS T score -5.0; >2 vertebral fractures; disease or medication affecting bone metabolism	PBO, n=982 IBN2.5mg/d, n=982 IBN 20mg eod, 12 doses/m, n=982 *Adjuvant:* Both groups, calcium 500 mg/d and vitamin D 400IU/d	36 months Lateral radiographs performed annually, BMD assessed every 6 months for 2 years, then annually	*Primary:* new morphometric vertebral fracture *Secondary:* worsening fractures, clinical vertebral and osteoporotic non vertebral fractures; change in BMD at LS and femur; biomarkers	*Fractures:* Lateral radiographs of thoracic the spine. Diagnosis of fracture based on morphometric criteria confirmed by qualitative assessment by radiologist. Morphometric fracture – height reduction at least 20% and 4mm decrease *BMD:* DXA (Hologic QDR)
Lester 2008[76] (ARIBON) UK. Multicentre RCT, 2 centres Astra Zeneca and Roche	*Inclusion:* postmenopausal women with a histologically confirmed diagnosis of oestrogen receptor –positive breast cancer. Patients classified as osteopenic (T scores of >-2.5 and <-1.0 either at the LS and TH) were randomized *Exclusion:* menopause was induced chemotherapy or drug therapy; concurrent administration; abnormal renal function, disorders of bone metabolism, and previous bilateral hip fractures prostheses.	PBO, n=25 IBN150mg/m, n=25 *Adjuvant:* Both groups, anastrozole 1 mg/d, calcium 500 mg/d and vitamin D 400IU/d	24 months BMD assessed at 12 and 24 months	*Primary:* change in BMD at the LS and TH *Secondary:* changes in bone resorption and formation markers and adverse events, including any fracture	*Fractures:* recorded as adverse events (assessment method not reported) *BMD:* DXA – Lunar DPX

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
McClung 2009[82] USA. Multicentre RCT, 10 centres Roche	*Inclusion:* postmenopausal women aged 45–60 years with baseline mean lumbar spine (LS) BMD T-score between -1.0 and -2.5 and baseline T-score>-2.5 in total hip (TH), trochanter (TR) and femoral neck (FN) with no prior vertebral fractures. *Exclusion:* Women with prevalent vertebral or low-trauma osteoporotic fractures; patients receiving treatment affecting bone metabolism.	PBO, n=83 IBN150mg/m, n=77 *Adjuvant:* Both groups, 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS (L2–L4) BMD *Secondary:* Change in FN, total hip and trochanter BMD change in bone resorption marker serum	*Fractures:* fractures were confirmed by radiograph and reported as adverse events. *BMD:* DXA - (Hologic Inc., Bedford, MA).
Ibandronate dose ranging trials					
Delmas 2006 [49] (DIVA) USA, Canada, Mexico, Europe, Australia and South Africa Multicentre non-inferiority RCT, 53 centres Hoffman-La Roche and GlaxoSmithKline	*Inclusion:* Postmenopausal women 55–80 years of age; at least 5 years since menopause with osteoporosis (mean lumbar spine [L2-L4] BMD T score < -2.5 to -5.0) *Exclusion:* prior treatment with bisphosphonates or any other drug affecting bone metabolism; upper GI disease; renal impairment	IBN2.5mg/d, n=470 IBN2mg/iv, 2/m, n=454 IBN3mgiv, 3/m, n=471 *Adjuvant:* All groups, 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS (L2–L4) BMD year 1 *Secondary:* change in LS (L2–L4) BMD year 2 and BMD at proximal femur; bone markers	*Fractures:* Clinical vertebral and non-vertebral fractures were monitored from adverse event reporting (all fractures were confirmed radiographically). *BMD:* DXA on GE Lunar [Madison, WI, USA] and Hologic [Bedford, MA, USA]
Eisman 2008 [50] (DIVA) (year 2 data)			24 months		

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Miller 2005[47] (MOBILE) RCT phase III, non-inferiority study, involving 65 centres in the United States, Canada, Europe, Australia, South Africa, Mexico, and Brazil Hoffman-La Roche and GlaxoSmithKline	*Inclusion:* Postmenopausal women 55–80 years of age; at least 5 years since menopause with osteoporosis (mean lumbar spine [L2-L4] BMD T score < -2.5 and -5.0) *Exclusion:* Patients with uncontrolled active or recurrent peptic ulcer disease were excluded. Additional exclusion criteria were a disease, disorder, or therapy known to influence bone metabolism; prior treatment with bisphosphonates; fluoride treatment and renal	IBN2.5mg, n=402 IBN50mg. 2 doses/m, n=402 IBN100mg/m, n=404 IBN150mg/m, n=401: *Adjuvant:* Both groups, calcium 500mg/d plus vitamin D ≤400 IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS (L2–L4) BMD *Secondary:* Change in TH, trochanter and FN BMD	*Fractures:* Clinical vertebral and non-vertebral fractures were recorded as adverse events. *BMD:* DXA on GE Lunar [Madison, WI, USA] and Hologic [Bedford, MA, USA]
Reginster 2006 [48] (MOBILE) (year 2 data)			24 months		

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Risedronate vs. placebo					
Boonen 2009[60] Eastern and Western Europe, Lebanon, Australia, and the United States. Phase III multicentre RCT Procter & Gamble Pharmaceuticals and Sanofi-Aventis Pharmaceuticals	*Inclusion:* Men ≥30 yr. of age with osteoporosis including LS T-score ≤ -2.5 and FN T-score ≤ -1 SD or LS T-score ≤ -1 and FN T-score ≤ -2 SD. *Exclusion:* Men with secondary osteoporosis except those with primary hypogonadism who declined testosterone replacement therapy.	PBO, n=93 RIS35mg/w, n=191 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400-500IU/d	24 months X-rays taken at 12 and 12 months; BMD assessed at 6, 12 and 24 months	*Primary:* change in LS BMD at month 24 *Secondary:* change in LS and proximal femur BMD at months 6, 12, and 24; incidence of new vertebral fractures; incidence of clinical fractures (vertebral and Non-vertebral) reported as AEs at months 12 and 24.	*Fractures:* New vertebral fractures were determined by X-ray using a semiquantitative method Clinical vertebral and Non-vertebral fractures were reported as adverse events *BMD:* DXA (Hologic)
Choo 2011[64] Canada. RCT, number centres not reported AstraZeneca Pharmaceuticals	*Inclusion:* non-metastatic prostate cancer patients receiving radiotherapy plus 2-3 years of Androgen Ablation Therapy. All had LS T scores > -2.5	PBO, n=52 RIS35mg/w, n=52 *Adjuvant:* Both groups, calcium and vitamin D supplements (amount not reported)	24 months BMD assessed at 12 and 24 months	*Primary:* change in LS, FN and proximal femur BMD, biomarkers for bone turnover	*Fractures*: not an outcome BMD of the lumbar spine, proximal femur, and femoral neck were measured by DXA at baseline, year 1 and year 2

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Cohen 1999 [65] USA Multicentre RCT, 28 centres Procter & Gamble / NIH	*Inclusion:* Men and women aged 18-85 years old on glucocorticoids ≥ 7.5mg/day within 3 months; women at least 1 year postmenopausal *Exclusion:* History of hyperparathyroidism, hyperthyroidism or osteomalacia, use of drugs known to affect bone metabolism	Premenopausal women: PBO, n=52 RIS5mg/d, n=49 Postmenopausal women PBO, n=15 RIS5mg/d, n=14 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	12 months X-rays and BMD assessed at 12 months	*Primary:* Change of BMD at the LS BMD FN BMD, and femoral trochanter BMD *Secondary:* Fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* Quantitative morphometry was used to identify prevalent (baseline) and incident (new) vertebral fractures. A new (incident) vertebral fracture was defined as a decrease of ≥15% (for intact vertebrae at baseline) or a decrease of ≥4 mm (for fractured vertebrae at baseline) *BMD:* DXA - Hologic (Waltham, MA) or Lunar (Madison, WI)
Fogelman 2000 [68] (BMD-MN) France, the UK, the Netherlands, Belgium, and Germany Multicentre RCT, 13 centres Procter & Gamble and Aventis	*Inclusion:* Women up to 80 years of age. Postmenopausal for at least 1 year; mean lumbar spine (L1-L4) T score of -2 or less. *Exclusion:* History of hyperparathyroidism, hyperthyroidism or osteomalacia, use of drugs known to affect bone metabolism	PBO, n=180 RIS5mg/d, n=179 Also evaluated RIS2.5mmg/d, n=184 *Adjuvant:* Both groups, calcium1000mg/d	24 months BMD assessed at 6, 12, 18, and 24 months; X-ray at 24 months	*Primary:* Incidence of vertebral and non-vertebral fractures; and percentage change of BMD of the spine *Secondary:* Adverse events; and biochemical markers of bone turnover.	*Fractures:* non-vertebral fractures and vertebral fractures assessed as adverse events by radiographs. A vertebral body was considered to be fractured if any of the vertebral height ratios fell below 3 SD of the mean for the study population, *BMD:* Lunar Corp. (Madison, WI, USA) or Hologic, Inc. (Waltham, MA)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Hooper 2005 [74] Australia Multicentre RCT, 11 centres Procter & Gamble and Aventis	*Inclusion:* Postmenopausal women for 6 to 36 months, with lumbar-spine BMD of greater than -2.5 SD (< 0.76 g/cm2 *Exclusion:* History of hyperparathyroidism, hyperthyroidism, or osteomalacia; treatment with bone agents likely to affect bone metabolism.	PBO, n=126 RIS5mg/d, n=129 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	24 months BMD assessed at 3, 6, 12, 18 and 24 months; X-ray at 24 months	*Primary:* Changes in LS BMD *Secondary:* Change of BMD at the FN, and trochanter; incidence of vertebral and non-vertebral fractures; adverse events.	*Fractures:* Prevalence and incidence vertebral fractures assessed by morphometric analysis. An incident fracture was considered evident if anterior/middle vertebral height was ≥15% of normal vertebrae height *BMD:* Hologic (Waltham, MA) or Lunar (Madison, WI)
Harris 1999 [72] (VERT-NA) USA Multicentre RCT, 110 centres Procter & Gamble	*Inclusion:* Ambulatory women no older than 85 years, ≥5 years since menopause, with at least 1 vertebral fracture at baseline. *Exclusion:* Use of drugs known to affect bone metabolism.	PBO, n=815 RIS5mg/d, n=813 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	36 months X-ray at 12, 24 and 36 months; BMD assessed every 6 months	*Primary:* Incidence of vertebral and non-vertebral fractures; and percentage change of BMD of the spine *Secondary:* Adverse events; and biochemical markers of bone turnover.	*Fractures:* Quantitative and semiquantitative assessment was used to assess prevalent (baseline) and incident fractures. Fracture was considered evident if anterior/middle vertebral height was ≤0.8 of posterior. *BMD:* Lunar (Madison, WI) or Hologic (Waltham, MA)
Ste-Marie (2004)[101] (VERT-NA extension)	Women who had successfully completed the original 3-year study and who had undergone baseline and month-36 iliac crest biopsies were eligible to enrol. Women continued on their assigned treatments (placebo or risedronate) for an additional 2 years	PBO, n=42 RIS5mg/d, n=44	60 months	*Primary:* Histologic and Histomorphometric Assessments *Secondary:* Change in BMD	*Fractures:* recorded as adverse events

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Reginster 2000 [87] (VERT-MN) European and Australian centres Multicentre RCT, no. centres NR Procter & Gamble and Hoechst Marrion Roussel	*Inclusion:* Ambulatory women up to 85 years and at least 5 years postmenopausal; had at least 2 radiographically confirmed vertebral fractures. *Exclusion:* Receiving treatment known to affect bone metabolism	PBO, n=407 RIS5mg/d, n=407 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	36 months BMD assessed every 6 months, X-rays every 12 months	*Primary:* Changes in LS BMD *Secondary:* Change of FN BMD of the FN and trochanter BMD; incidence of vertebral and non-vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* Quantitative and semiquantitative assessment was used to assess prevalent (baseline) and incident fractures. Fracture was considered evident if anterior/middle vertebral height was ≥15% of normal vertebrae height. *BMD:* Lunar (Madison, WI) or Hologic (Waltham, MA)
Sorensen 2003 [102] (VERT-MN extension) USA Multicentre RCT, 29 centres Procter & Gamble	*Inclusion:* Women remained on the treatments (placebo or risedronate, 5 mg daily) to which they had originally been assigned. Blinding was maintained for the patients and clinical centre personnel throughout the 5 years of study.	PBO, n=130 RIS5mg/d, n=135 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	60 months	*Primary:* Incidence of vertebral fractures *Secondary:* Incidence of non-vertebral fractures; changes in LS and FN BMD and, FN, femoral trochanter and radius; biochemical markers of bone turnover; adverse events.	

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Leung 2005 [77] China Multicentre RCT, 4 centres Aventis Pharma	*Inclusion:* postmenopausal for 5 or more years with spine BMD at L1– 4 <2.5 SD of the local peak young mean value. *Exclusion:* any medical conditions or medication known to affect bone metabolism	PBO, n=34 RIS5mg/d, n=31 *Adjuvant:* Both groups, calcium 500mg/d plus vitamin D 400 IU/d	12 months BMD assessed at 3, 6 and 12 months	*Primary:* Change in FN, LS, TH and trochanter BMD; bone marker *Secondary:* not reported	*Fractures:* not an outcome *BMD*: DXA (Hologic QDR 4500 plus, Hologic Inc., Waltham, MA, USA).
McClung 2001[80] USA Multicentre RCT, 183 centres Procter & Gamble / Aventis	*Inclusion:* Women ≥70 years old; Low BMD at the femoral neck T score lower than -4 or lower than -3 with at least 1 non-skeletal risk factor for hip fracture. *Exclusion:* Any major illness, history of another metabolic bone disease, bilateral hip fracture, recent use of drugs known to affect bone	Women 70–79 years: PBO, n=1821 RIS2.5mg/d, n=1812 RIS5mg/d, n=1812 Women ≥80 years: PBO, n=1313 RIS2.5mg/d, n=1281 RIS5mg/d, n=1292 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	36 months BMD assessed every 6 months	*Primary:* Change in LS BMD *Secondary:* Change in BMD of the FN, proximal femur, trochanter, radius; vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* radiographically confirmed hip fractures and non-vertebral osteoporotic fractures. Non-vertebral osteoporotic fractures, defined as all radiographically confirmed fractures of the wrist, leg, humerus, hip, pelvis, or clavicle. *BMD: DXA* - (Lunar, Madison, Wis., or Hologic, Waltham, Mass.

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Reid 2000 [88] UK Multicentre RCT, 23 centres Procter & Gamble and/ Hoechst Marrion Roussel	*Inclusion:* Ambulatory men and women 18-85 years, who had taken glucocorticoids for at least 6 months. *Exclusion:* History of hyperparathyroidism, hyperthyroidism, or osteomalacia; treatment with bone agents likely to affect bone metabolism	PBO, n=96 RIS5mg/d, n=100 *Adjuvant:* Both groups, vitamin D 400 IU/d calcium 1000mg/d	12 months BMD assessed at 6 and 12 months; X-ray at 12 months	*Primary:* Change in LS BMD *Secondary:* Change in BMD of the FN, proximal femur, trochanter, radius; vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* incident fractures were identified using quantitative morphometry defined as a reduction of ≥15% in vertebral height in a previously intact vertebra or a reduction of ≥4mm in a previously fractured vertebra *BMD:* DXA - Lunar (Madison, WI, USA.) or Hologic (Waltham, Massachusetts, U.S.A.)
Ringe 2006[91] Germany. Single-centre RCT Sponsor not reported	*Inclusion:* Men with primary or secondary osteoporosis with or without pre-existing prevalent vertebral fractures. Osteoporosis was defined as a LS (BMD) T-score of ≤-2.5 SD and FN BMD T-score of ≤-2.0 relative to a healthy young adult male. Primary OP; secondary OP: PBO, 92 (58.2%); 66 (41.8%) RIS5mg/d, 94 (59.5%); 64 (40.5%) *Exclusion:* Patients with known hypersensitivity to bisphosphonates, severe impairment of renal function, hypocalcaemia and a history of bisphosphonate or fluoride pre-treatment	PBO, n=158 RIS5mg/d, n=158 *Adjuvant:* PBO with fractures, calcium 500mg/d and alfacalcidol 1000mg/d PBO without factures, calcium 800mg/d and vitamin D 1000IU/d	12 months BMD and X-ray at 12 months	*Primary:* Change in LS BMD *Secondary:* incidence of new vertebral fractures; change in FN and TH BMD; change in body height; course of back pain; and the incidence of non-vertebral fractures.	*Fractures:* Radiographic X-rays of the spine. Assessment of vertebral fracture was performed using the semi-quantitative technique *BMD:* DXA (Lunar Corp., Madison, WI, USA).
Ringe 2009 [103] Follow-up to Ringe 2006[91]		PBO, n=158 RIS, n=158	24 months		

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Taxel 2010[97] USA. RCT, number centres not reported Proctor and Gamble/and Aventis	*Inclusion:* Men aged >55 years and within a month of receiving an initial injection of ADT for prostate cancer *Exclusion:* metastatic bone disease, chronic kidney, gastrointestinal or liver diseases, a previous cancer diagnosis, metabolic bone disorders medications that interfere with bone metabolism.	PBO, n=20 RIS35mg/w, n=20 *Adjuvant:* Both groups, calcium 600 mg/d and vitamin D 400IU/d	6 months BMD assessed at 6 months	*Primary:* FN and TH BMD *Secondary:* change in bone markers	*Fractures:* not an outcome *BMD* DXA (Lunar DXA-IQ, Madison, WI, USA)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Zoledronate vs. placebo					
Black 2007[58] (HORIZON-PFT) International. Multicentre RCT. Number centres not reported. Novartis Pharma	*Inclusion:* Postmenopausal women between the ages of 65 and 89 with FN BMD T score of -2.5 or less, with or without evidence of existing vertebral fracture, or a T score of -1.5 or less, with radiologic evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Use of hormone therapy, raloxifene, calcitonin, tibolone, tamoxifen, ehydroepiandrosterone ipriflavone, and medroxyprogesterone was allowed. Patients in Stratum I (n=6113) were not taking any osteoporosis medications at the time of randomization, whereas patients in Stratum II (n=1652) were all taking an allowed medication. *Exclusion:* previous use of parathyroid hormone., sodium fluoride, anabolic steroids, growth hormone, glucocorticoids, or strontium	PBO, n=3876 ZOL5mg/y, n=3889 *Adjuvant:* Both groups, calcium 1000 -1500mg/d and vitamin D 400-1200IU/d	36 months X-ray at 12, 24, and 36 months in Stratum I; baseline and 36 months in Stratum II; BMD assessed at 6, 12, 24 and 36 months	*Primary:* Stratum II, vertebral fractures Strata I & II, hip fracture. *Secondary:* any non-vertebral fracture, any clinical fracture, and clinical vertebral fracture. Changes in LS, FN and TH BMD; changes in markers of bone resorption and formation.	*Fractures:* Spinal lateral radiographs were, vertebrae from T4 to L4 were evaluated with the use of quantitative morphometry and standard methods. Incident morphometric vertebral fractures were defined as a reduction in vertebral height of at least 20% and 4 mm by quantitative morphometry, confirmed by an increase of one severity grade or more on semiquantitative analysis. Clinical fracture reports were obtained from patients at each contact. Non-vertebral fracture reports required central confirmation. Excluded were fractures of the toe, facial bone, and finger and those caused by excessive trauma. *BMD*: DXA – model not reported. Measurements of bone mineral density at the lumbar spine were obtained for a subgroup of patients.
Reid 2010[104] (HORIZON-PFT)				Adverse events	

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Lyles 2007[79] (HORIZON-RFT) International. Multicentre RCT number centres not reported Novartis Pharma	*Inclusion:* Men and women 50 years of age or older within 90 days after surgical repair of a hip fracture sustained with minimal trauma; ambulatory prior to fracture. *Exclusion:* calculated low creatinine clearance, low serum calcium, active cancer, metabolic bone disease, and a life expectancy of less than 6 months	PBO, n=1062 ZOL5mg/y, n=1065 *Adjuvant:* Both groups, calcium 1000 -1500mg/d and vitamin D 800-1200IU/d	36 months BMD assessed every 12 months	*Primary:* new clinical fractures excluding facial and digital fractures and fractures in abnormal bone (e.g., bone containing metastases). *Secondary:* BMD of the non-fractured hip; new vertebral, non-vertebral, and hip fractures; safety	*Fractures:* Lateral radiography of the chest and lumbar spine. A non-vertebral fracture (not a vertebral, facial, digital, or skull fracture) was confirmed when a radiograph, a radiographic report, or a medical record documented a new fracture. A new clinical vertebral fracture was defined as new or worsening back pain with a reduction in vertebral body height of 20% (grade 1) or more, as compared with baseline radiographs, or a reduction in vertebral body height of 25% (grade 2) or more if no baseline radiograph was available. *BMD:* DXA – model not reported
Adachi 2011[105] (HORIZON-RFT)				Quality of life	

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Boonen 2012[61] Europe, South America, Africa, and Australia. RCT, number centres not reported Novartis	*Inclusion:* Men 50 to 85 years of age who had primary osteoporosis or osteoporosis associated with low testosterone levels with BMD T score ≤–1.5 at TH or FN and one to three prevalent vertebral fractures Men without fractures were eligible if they had a bone mineral density T score ≤–2.5 at TH, FN or LS *Exclusion:* four or more prevalent vertebral fractures; low serum vitamin D, renal insufficiency, hypercalcaemia or hypocalcaemia; hypersensitivity to bisphosphonates; medication affecting bone metabolism	PBO, n=611 ZOL5mg/y, n=588 *Adjuvant:* Both groups, calcium 1000-1500 mg/d and vitamin D 800-1200IU/d	24 months X-ray at 12 and 24 months; BMD assessed at 6, 12 and 24 months	*Primary:* proportion of men with one or more new morphometric vertebral fractures *Secondary:* proportion of men with one or more new morphometric vertebral fractures; one or more new moderate-to-severe, or new or worsening morphometric vertebral fractures; change in height; the time to first clinical fracture (vertebral or Non-vertebral); change in LS, FN and TH BMD; bone-turnover markers; safety	*Fractures:* Vertebral fractures were assessed by means of quantitative vertebral morphometry performed on lateral thoracic and lumbar spine, incident vertebral fracture was assessed by means of morphometry and defined as a reduction in vertebral height of 20% or more and 4 mm or more. Clinical fractures (vertebral and Non-vertebral) were reported by participants at each visit and were verified by radiographic report or surgical notes. Only confirmed fractures were included in the analysis *BMD:* DXA – model not reported. BMD and bone markers were analysed in a subgroup of 100 or more participants.

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
McClung 2009 [81] USA and France. Multicentre RCT, 25 centres Novartis	*Inclusion:* Women aged 45 and older who were postmenopausal LS BMD T score less than -1.0 and more than -2.5 and FN T score greater than -2.5 *Exclusion:* Participants with >1 vertebral fracture or any grade 2 or 3 vertebral fracture. Participants with low vitamin D, renal insufficiency, hyper- or hypocalcaemia, treatment medications affecting bone metabolism	PBO, n=202 ZOL5mg/y, n=198 *Adjuvant:* Both groups, calcium 500-1200 mg/d and vitamin D 400-800IU/d	24 months BMD assessment time points not reported	*Primary:* change in LS BMD at 12 months *Secondary:* change TH< FN, trochanter and distal radius at 12 and 24 months; bone markers	*Fractures:* not an outcome *BMD:* DXA Hologic or GE Lunar machine.
Head-to-head – Alendronate vs. Ibandronate					
Miller 2008[83] (MOTION) The Americas, USA, Europe and South Africa. Multicentre RCT, 65 centres Hoffman La-Roche Ltd and GlaxoSmithKline	*Inclusion:* postmenopausal women aged 55 to <85 with LS (L2–L4) BMD T-score <–2.5 and ≥–5.0 SD *Exclusion:* upper GI disease, any diseases or medications known to influence bone metabolism.	ALN70mg/w, n=873 IBN150mg/m, n=887 *Adjuvant:* Both groups, calcium 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS and TH BMD. *Secondary:* change in trochanter BMD; bone markers	*Fractures:* recorded as adverse events (assessment method not reported) *BMD:* DXA – model not reported
Head-to-head – Alendronate vs. Risedronate					
Atmaca 2006 [56] Turkey RCT, n centres not reported Sponsor not reported	*Inclusion:* late postmenopausal women with osteoporosis with a mean age of 66.3 y (range, 60–85 y) and a T-score less than –2.5 *Exclusion:* any medical conditions or medication known to affect bone metabolism	RIS5mg/d, n=14 ALN10mg/d, n=14 *Adjuvant:* Both groups, calcium 600 mg/d and vitamin D 400IU/d	12 months BMD assessment time point not reported	*Primary:* change in FN, LS and distal radius BMD; bone markers *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA – Hologic QDR

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Muscoso 2004[84] Italy RCT, n centres not reported Sponsor not reported	*Inclusion:* osteoporotic female population submitted to a treatment with antiresorption drugs *Exclusion:* not reported	RIS5mg/d, n=1000 ALN10mg/d, n=100 Other treatments were: clodronate, n=800 and raloxifene, n=100 *Adjuvant:* all groups, calcium 1000 mg/d and vitamin D 800IU/d	24 months BMD assessment time point not reported	*Primary:* change in LS BMD; fractures *Secondary:* not reported	*Fractures:* not reported *BMD:* DXA – Lunar DPX
Sarioglu 2006[94] Turkey RCT, n centres not reported Sponsor not reported	*Inclusion:* postmenopausal women with osteoporosis *Exclusion:* Patients over 75 years and taking treatment for osteoporosis. The presence of any disease which interferes with bone metabolism, recent use of drugs known to affect bone metabolism and history of esophagitis and peptic ulcer were also accepted as exclusion criteria.	RIS5mg/d, n=25 ALN10mg/d, n=25 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400IU/d	12 months BMD assessment time point not reported	*Primary:* change in hip BMD *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA – Lunar DPX

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Rosen 2005[92] (FACT) USA Multicentre RCT, 78 centres Merck	*Inclusion:* Postmenopausal women≥40years or ≥25y if surgically menopausal. BMD T score ≤-2.0 SD in at least 1 of the 4 sites (total hip, hip trochanter, femoral neck, or posterior lumbar spine) *Exclusion:* Hypocalcaemia, hypovitaminosis D, metabolic bone disease; bisphosphonates w/in 1y or for ≥2y w/in 5y; use of PTH w/in1y. Had taken oestrogen, oestrogen analogues within 6 months	ALN70mg/w, n=520 RIS35mg/w, n=533 Both groups, 1000 mg calcium and 400 IU vitamin D	12 months BMD assessed at 6 and 12 months	*Primary:* Change trochanter BMD *Secondary:* Change in BMD at total hip, FN, total hip and LS	*Fractures:* incidence of clinical fracture recorded as adverse events (assessment method not reported) *BMD:* Hologic (Waltham, MA) or Lunar (Madison, WI)
Bonnick 2005[106] (FACT) (Extension to Rosen 2005[92]) USA Multicentre RCT, 72 of the original 78 centres Merck	*Inclusion:* Postmenopausal women≥40years or ≥25y if surgically menopausal. BMD T score ≤-2.0 SD in at least 1 of the 4 sites (total hip, hip trochanter, femoral neck, or posterior lumbar spine) *Exclusion:* Hypocalcaemia, hypovitaminosis D, metabolic bone disease; bisphosphonates w/in 1y or for ≥2y w/in 5y; use of PTH w/in1y. Had taken oestrogen, oestrogen analogues within 6 months	ALN70mg/w, n=411 RIS35mg/w, n=414 Both groups, 1000 mg calcium and 400 IU vitamin D	Extension to 24 months	*Primary:* Change trochanter BMD *Secondary:* Change in BMD at total hip, FN, total hip and LS	*Fractures:* Clinical fractures that occurred during the trial, regardless of association with trauma or skeletal site, were reported by investigators as clinical AEs (assessment method not reported) *BMD:* Hologic (Waltham, MA) or Lunar (Madison, WI)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Reid 2006[89] (FACTS) Europe, the Americas and Asia-Pacific. Multicentre RCT , 75 centres Merck & Co., Inc.	*Inclusion:* Postmenopausal >40 years of age with low bone density (-2.0 SD below the young normal mean at LS< FN or TH *Exclusion:* hypocalcaemia, hypovitaminosis D, or metabolic bone diseases, use of oestrogen, oestrogen analogues, tibolone or anabolic steroids, bisphosphonates, or parathyroid hormone	ALN70mg/w, n=468 RIS35mg/w, n=468 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400IU/d	12 months BMD assessed at 6 and 12	*Primary:* change in trochanter BMD *Secondary:* change in LS, TH and FN BMD	*Fractures:* Fractures were reported as adverse events whether or not they were associated with trauma and without requirements of radiographic confirmation or adjudication *BMD:* DXA -using Hologic or Lunar densitometers
Reid 2008[107] (FACTS) (Extension to Reid 2006[89]) Seventy-two of the original 75 international sites Merck & Co., Inc.	*Inclusion:* all eligible women maintained their original randomised, blinded treatment allocation from year 1	ALN70mg/w, n=403 RIS35mg/w, n=395 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400IU/d	24 months		
Head-to-head – Zoledronate vs. Alendronate					
Hadji 2010[108] (ROSE)				*Primary:* Quality of Life and compliance	

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Hadji 2012[71] (ROSE) Germany Multicentre RCT, 95 centres Novartis Pharma	*Inclusion:* women aged 55–90 years who were considered postmenopausal with BMD T-score ≤-2.0 at TH or LS *Exclusion:* Patients who had received prior therapy with bisphosphonates, parathyroid hormone, strontium ranelate, raloxifene, calcitonin, high-dose glucocorticoids, patients with a fracture within 6 months secondary osteoporosis, primary hyperparathyroidism, Patients with inappropriate blood chemistry.	ZOL5mg/y, n=408 ALN70mg/w, n=196 *Adjuvant:* Both groups, calcium 1200 mg/d and vitamin D 800IU/d	12 months	*Primary:* to assess if zoledronic acid was superior to alendronate in reducing serum NTx levels. *Secondary:* comparison of P1NP levels ; safety and tolerability	*Fractures and BMD:* not outcomes assessed by the trial (assessed bone markers and quality of life)
Head-to-head – Zoledronate vs. Risedronate					
Reid 2009[90] (HORIZON) Australia, EU countries including UK, Hong Kong and USA. Multicentre RCT, 54 centres Novartis Pharma	*Inclusion:* Men and women aged 18–85 receiving at least 7.5 mg oral prednisolone daily (or equivalent) and were expected to receive glucocorticoids for at least another 12 months. *Exclusion:* previous treatment drugs that affect the skeleton, low serum vitamin D history of cancer or parathyroid disease, and renal impairment.	ZOL5mg/y treatment, =272; prevention, n=144 RIS5mg/d - treatment, n=273; prevention, n=144 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400-1200IU/d	12 months BMD assessed at 6 and 12 months; X-ray at 12 months	*Primary:* change in LS BMD *Secondary:* change in BMD at FN, TH, trochanter, and distal radius; occurrence of thoracic and lumbar vertebral fractures	*Fractures:* thoracic and lumbar vertebral fractures were defined according to semiquantitative methods *BMD:* Hologic (Waltham, MA, USA) or GE Lunar (Madison, WI, USA)

ALN, alendronate; BMD, bone mineral density; DXA, dual X-ray absorptiometry; eod, every other day; FN, femoral neck; IBN, ibandronate; LS, lumbar spine; mg/d, milligrams per day; mg/m, milligrams per month; mg/iv, milligrams intravenous; mg/y, milligrams per year; NTx, N-telopeptide of collagen type I; P1NP, procollagen 1 C terminal extension peptide; PBO, placebo; PTH, parathyroid hormone; RCT, randomised controlled trial; RIS, risedronate; IU/d, international units per day; SD, standard deviation; TH, total hip; ZOL, zoledronate; 2/m, twice per month; 3/m, three times per month

Trial acronyms: ARIBON, reversal of anastrozole (ARImidex) induced bone loss with oral monthly ibandronate (BONdronat) treatment during adjuvant therapy for breast cancer; BONE, iBandronate Osteoporosis vertebral fracture trial in North America and Europe; DIVA, Dosing IntraVenous Administration; FACT, Fosamax Actonel Comparison Trial;

FACTS, Fosamax Actonel Comparison Trial international study; FIT, Fracture Intervention Trial; FOSIT, FOSamax International Trial; HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Recurrent Fracture Trial; ROSE, Rapid Onset and Sustained Efficacy; MOBILE, Monthly Oral iBandronate In LadiEs; MOTION, Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention; VERT-NA, Vertebral efficacy with Risedronate Therapy-North American; VERT-MN, Vertebral efficacy with Risedronate Therapy-Multi National

Table 5: Characteristics of participants in included RCTS

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Alendronate vs. placebo				
Adami 1995[55] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 59 (6); 11 (8) ALN10mg/d, 59 (6); 12 (7) *Height, weight, BMI (estimated):* PBO, 160cm (6); 60kg (8); 23.4 ALN10mg/d, 160cm 60kg (7); 23.4	None reported	*Current smokers:* PBO, 7/71 (9.9%) ALN10mg/d, 13/68 (19.1%)	*Fractures:* 5% of all participants had prevalent vertebral fractures *FN BMD cm^3:* PBO, non-Lunar, 0.65 (0.09); Lunar, 0.76 (0.08) ALN10mg/d, non-Lunar, 0.65 (0.09); Lunar, 0.71 (0.09)
Black 1996[57] (FIT I) Women with PMO	*Male/female:* 100% female *Race*: All, Caucasian 97%; Asian 1%; African-American 1% *Age*: PBO, 71.0 (5.6) ALN10mg/d, 70.1 (5.6) *BMI:* PBO, 25.6 (4.2) ALN10mg/d, 25.5 (4.2)	None reported	*Smokers:* PBO, Current 10%; ever 35%; never 54% ALN10mg/d, Current 10%; ever 35%; never 52%	*Fractures % with 1, 2 or ≥3:* PBO, 1, 68%; 2, 17%; ≥3, 15% ALN10mg/d, 1, 70%; 2, 17%; ≥3, 13% *FN BMD cm^3:* PBO, 0.56 (0.07) ALN10mg/d, 0.57 (0.07)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Cummings 1998[66] (FIT II) Women with PMO	*Male/female:* 100% female *Race*: All, Caucasian 97% *Age*: PBO, 67.7 (6.1) ALN10mg/d, 67.6 (6.2) *Height; BMI:* PBO, 160 (6.0), 25.0 (4.0) ALN10mg/d, 161 (6.0), 24.9 (3.9)	None reported	*Smokers:* PBO, Current 10%; ever 35%; never 54% ALN10mg/d, Current 10%; ever 35%; never 52%	*Fracture since age 45y :* PBO, 776/2218 (35%) ALN10mg/d, 797/2214 (36%) *FN BMD cm^3:* PBO, 0.59 (0.06) ALN10mg/d, 0.59 (0.06) *FN SDs >2.0, 2.0-2.5, 1.5-2.0 below peak %:* PBO, 36.6%, 32.0%, 31.4% ALN10mg/d, 37.0%, 32.8%, 30.2%
Bone 2000[59] Women with PMO	*Male/female:* 100% female *Race*: PBO, Caucasian 44/50 (88%); other 6/50 (12%) ALN10mg/d, Caucasian 85/92 (92%); other 7/92 (8%) *Age; yrs. since menopause*: PBO, 62 (8); 23 (11) ALN10mg/d, 61 (8); 22 (8) *Height, weight, BMI:* Not reported	None reported	Not reported	Not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Carfora 1998[62] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: not reported *Height, weight, BMI:* Not reported	None reported	Not reported	Not reported
Chesnut 1995[63] Women with PMO	*Male/female:* 100% female *Race*: All, Caucasian 184 (98%); Asian 4 (2%) *Age; yrs. since menopause*: PBO, 63.6 (7.1); 16.9 (7.7) ALN all doses, 62.9 (6.1); 15.0 (6.9) *Height, weight:* PBO, 160.6cm (5.9); 61.6kg (9.8) ALN all doses, 161.6cm (6.8); 63.7kg (9.4)	None reported	Not reported	Not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Dursun 2001[67] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: Ca 1000mg/d, 60.26 (8.58); 14.32 (7.96) ALN10mg/d+Ca, 60.26 (8.58); 14.88 (7.60) *Height; weight; BMI:* Ca 1000mg/d, 154.10cm (4.78); 66.41kg (11.53); 28.62 (5.52) ALN10mg/d+Ca, 154.10cn (4.78); 66.41kg (11.53); 28.62 (5.52)	None reported	Not reported	*FN BMD cm^3:* Ca 1000mg/d, 0.77 (0.1) ALN10mg/d+Ca, 0.74 (0.08)
Greenspan 2002[69] Women with PMO	*Male/female:* 100% female *Race*: All (n=327), Caucasian, 95% *Age;* All, 78.5 years (range 65 to 91) *Height; weight; BMI:* Not reported	None reported	Not reported	*Fractures:* 55% had a history of fracture (type not reported) *FN BMD cm^3*: not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Greenspan 2003[70] Women aged 65 or older	*Male/female:* 100% female *Race*: not reported *Age:* PBO, 72 (5) ALN10mg/d, 71 (4) *Height; weight; BMI:* PBO, 159cm (7); 69kg (18); 27 (6) ALN10mg/d, 159cm (6); 71kg (17); 28 (7)	None reported	Not reported	*Fracture since age 50y :* PBO, 31/93 (33%) ALN10mg/d, 36/93 (39%) *FN BMD cm^3:* PBO, 0.66 (0.10) ALN10mg/d, 0.66 (0.10)
Ho 2005[73] Women with PMO	*Male/female:* 100% female *Race*: 100% East Asian *Age; yrs. since menopause*: Ca 500mg/d, 62 (4); 12 (4.8) ALN10+Ca, 60.6 (5.5); 11.6 (5.8) *Height; weight; BMI (estimated):* Ca 500mg/d, 1.5m (0.3); 52kg (7.4); 23.1 ALN10+Ca, 1.52m (4.4); 51.8kg (8); 22.4	None reported	Not reported	*Prevalent vertebral fracture:* Ca 500mg/d, 10/29 (34%) ALN10+Ca, 12/29 (41%) *FN BMD cm^3:* Ca 500mg/d, 0.532 (0.069) ALN10+Ca, 0.583 (0.054) *FN BMD T-score:* Ca 500mg/d, -3.4 (0.7) ALN10+Ca, -2.2 (0.6)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Klotz 2013[75] (CORAL) Men with androgen deprivation bone loss in non-metastatic prostate cancer	*Male/female:* 100% male *Race*: not reported *Age*: PBO, 73.7 (8.6) ALN70mg/w, 73.5 (8.1) *Height; weight, BMI;* not reported	*Gleason prostate cancer score* :* PBO, Gleason 6, 15; Gleason 7, 34; Gleason 8, 18 ALN70mg/w, Gleason 6, 17; Gleason 7, 26; Gleason 8, 18 *ADT therapy:* Forty-two prior ADT regimens were reported in 34/183 (19%) all participants. Median duration of prior ADT 6.1m (range: 1.0-16.2).	*Smoking mean (SD) years; packs per day:* PBO, 23.4 (14.6); 0.94 (0.48) ALN70mg/w, 29.5 (16.2); 0.98 (0.49)	*Fractures:* Of the 47% who reported prior fracture, 1% had had a history of hip or vertebral fracture. Four participants in the alendronate group reported a family history of osteoporotic fracture. *FN BMD cm^3* :not reported. At baseline, 63 subjects (38%) had osteopenia (25 patients treated with alendronate and 38 treated with placebo) and 12 subjects (7%) had osteoporosis (3 patients treated with alendronate and 9 treated with placebo). The remaining ITT population was considered to have normal BMD for their age.
Liberman 1995[78] Seeman 1999[99] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 64; 17 ALN all doses, 64; 16 *BMI;* PBO, 24.1 ALN all doses, 24.2	None reported	Not reported	*Fractures at baseline:* PBO, Vertebral 75/355 (21.2%); non-vertebral 187/355 (52.6%) ALN all doses, Vertebral 106/526 (20.2%); non-vertebral 300/526 (57.0%) *FN BMD cm^3:* PBO, 0.6 ALN all doses, 0.6

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Orwoll 2000[85] Men with OP	*Male/female:* 100% male *Race*: not reported *Age*: PBO, 63 (12) ALN10mg/d, 63 (13) *BMI:* PBO, 25 (3) ALN10mg/d, 25 (3)	None reported	*Current smokers:* PBO, 23/95 (24.2%) ALN10mg/d, 28/146 (19.2%)	*Fractures at baseline:* PBO, Vertebral 52/95 (54.5%) ALN10mg/d, Vertebral 49/146 (33.7%) *FN BMD $cm^{3:}$*: not reported
Pols 1999[86] (FOSIT) Women with PMO	*Male/female:* 100% female *Race*: PBO, Caucasian 901/958 (94%) ALN10mg/d, Caucasian 893/950 (94%) *Age; yrs. since menopause*: PBO, 62.8 (7.4); 15.9 (8.4) ALN10mg/d, 62.8 (7.5); 15.8 (8.5) *Height; weight; BMI (estimated):* PBO, 158.5cm (6.8); 63.6kg (9.7); 25.3 ALN10mg/d, 158.6cm (7.0); 63.8kg (9.6); 25.4	None reported	Not reported	*Fractures:* not reported. *FN BMD cm^3:* PBO, 0.62 (0.08) ALN10mg/d, 0.63 (0.09)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Saag 1998[93] (extension Adachi 2001[100]) Men and women with Glucocorticoid-induced OP	*Male/female:* PBO, Men 52/159 (33%); Premenopausal women 40/159 (25%); Postmenopausal women, 67/159 (42%) ALN10mg/d, Men 44/157 (28%); Premenopausal women 30/157 (19%); Postmenopausal women, 83/157 (53%) *Race*: PBO, Caucasian 142/159 (89%); Other 17/159 (11%) ALN10mg/d, Caucasian 138/157 (88%); Other 19/157 (12%) *Age*: PBO, 54 (15) ALN10mg/d, 55 (15) *Height; weight; BMI (estimated):* PBO, 158.5cm (6.8); 63.6kg (9.7); 25.3 ALN10mg/d, 158.6cm (7.0); 63.8kg (9.6); 25.4	*Comorbidities:* PBO, Rheumatoid arthritis 43 (27%); Polymyalgia 24 (15%); Lupus 19 (12%); Pemphigus 12 (8%); Asthma 15 (9%); Inflammatory myopathy 10 (6%); Inflammatory bowel disease 8 (5%); Giant-cell arteritis 6 (4%); Sarcoidosis 5 (3%); Myasthenia gravis 12 (8%); COPD 3 (2%); Nephritic syndrome 2 (1%) ALN10mg/d, Rheumatoid arthritis 52 (33%); Polymyalgia 30 (19%); Lupus 12 (8%); Pemphigus 10 (6%); Asthma 12 (8%); Inflammatory myopathy 7 (4%); Inflammatory bowel disease 10 (6%); Giant-cell arteritis 5 (3%); Sarcoidosis 7 (4%); Myasthenia gravis 1 (1%); COPD 4 (3%); Nephritic syndrome 7 (4%) *Glucocorticoid dose — mg/d of prednisone or equivalent median (range):* PBO, 11 (5-120) ALN10mg/d, 10 (7-95) All, 34% of the postmenopausal women were taking oestrogen replacement therapy (not described)	Not reported	Not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Shilbayeh 2004[95] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 60.8 (1.4); 12.6 (1.4) ALN10mg/d, 57.8 (1.4); 10.6 (1.5) *BMI:* PBO, 30.83 (0.73) ALN10mg/d, 30.99 (1.08)	None reported	Not reported	*Fractures:* not reported. *FN BMD cm^3:* PBO, 0.73 (0.02) ALN10mg/d, 0.73 (0.02)
Smith 2004[96] Men and women with asthma and/or chronic obstructive airways disease	*Male/female:* PBO, 37/79 (47%) male ALN10mg/d, 37/66 (56%) male *Race*: not reported *Age*: PBO, n < 60, 21 (27%); 60-69, 19 (24%); 70+, 39 (49%) ALN10mg/d, n < 60, 12 (18%); 60-69, 24 (36%); 70+, 30, (46%) *Height; weight; BMI:* not reported	*Comorbidities:* All had airways disease (asthma and/or COAD) *Medications:* PBO, Inhaled glucocorticoids, 68 (86%); Calcium, 27 (34%); Thyroxine, 6 (8%); Maintenance oral glucocorticoids, 15 (19%); Calcitriol, 6 (8%); Theophylline, 12 (15%) ALN10mg/d, Inhaled glucocorticoids, 60 (91%); Calcium, 28 (42%); Thyroxine, 4 (6%); Maintenance oral glucocorticoids, 10 (15%); Calcitriol, 8 (12%); Theophylline, 13 (20%)	*Current smokers:* PBO, 69 (87%) ALN10mg/d, 54 (82%)	Not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Ibandronate vs. placebo				
Chesnut 2004[45]; Chesnut 2005[46] (BONE) Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 68.8; 20.8 IBN2.5mg/d, 68.7; 20.9 IBN 20mg eod, 12 doses/m, 68.7; 20.8 *Height; weight; BMI:* PBO, 159.7cm; 66.8kg; 26.2 IBN2.5mg/d, 160.2cm; 66.6kg; 26.0 IBN 20mg eod, 160.3cm; 66.7kg; 26.0	*Comorbidities*: reports pre-existing GI disorders were similar across groups *Medications:* reports use of non-steroidal anti-inflammatory agents (NSAIDS) was comparable across groups	Not reported	*Vertebral fractures 1, 2:* PBO, 906 (93%), 421 (43%) IBN2.5mg/d, 920 (94%), 433 (44%) IBN 20mg eod, 12 doses/m, 917 (94%), 413 (42%) *FN BMD cm^3:* not reported *FN BMD T score:* PBO, -2.0 (0.9) IBN2.5mg/d, -1.7 (0.8) IBN 20mg eod, 12 doses/m, , -1.7 (0.9)
Lester 2008[76] (ARIBON) Postmenopausal women with breast cancer	*Male/female:* 100% female *Race*: not reported *Age median (range)*: PBO, 67.5 (63.6-71.0) IBN150mg/m, 67.8 (58.9-73.4) *BMI median (range):* PBO, 30.83 (0.73) IBN150mg/m, 30.99 (1.08)	All had a histologically confirmed diagnosis of oestrogen receptor-positive breast cancer and commenced anastrozole at study entry	Not reported	Not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
McClung 2009[82] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 53.4 (3.8); 5.5 (5.8) IBN150mg/m, 53.7 (3.6); 5.3 (6.0) *BMI:* PBO, 27.4 (6.1) IBN150mg/m, 27.2 (5.0)	None reported	Not reported	*Fractures:* not reported. *FN BMD cm^3:* PBO, 0.729 (0.082 IBN150mg/m, 0.738 (0.085 *FN BMD T score:* PBO, -1.1 (0.7) IBN150mg/m, -1.0 (0.8)
Ibandronate dose ranging trials				
Delmas 2006[49] Eisman 2008[50] (DIVA) Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: IBN2.5mg/d, 65.5;18.0 IBN2mg/iv, 2/m, 66.6' 19.3 IBN3mgiv, 3/m, 65.6; 18.2 *Height; weight; BMI:* IBN2.5mg/d, 158.4cm; 63.4kg; 25.3 IBN2mg/iv, 158.1cm; 64.1kg; 25.6 IBN3mgiv, 3/m, 158.1cm; 63.9kg; 25.6	None reported	Not reported	*Fractures:* IBN2.5mg/d, 166/381 (43.7%) IBN2mg/iv, 2/m, 148/355 (41.8%) IBN3mgiv, 3/m, 156/355 (41.8%) *FN BMD cm^3:* not reported *FN BMD T score:* not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Miller 2005[47] Reginster 2006[48] (MOBILE) Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: IBN2.5mg, 65.8; 18.3 IBN50/50mg, 66.0; 18.7 IBN100mg, 66.2; 19.1 IBN150mg, 66.2; 18.3 *BMI:* IBN2.5mg, 25.9 IBN50/50mg, 25.8 IBN100mg, 25.9 IBN150mg, 25.5	None reported	Not reported	*History of previous fractures:* IBN2.5mg, 192 (48.9%) IBN50/50mg, 183 (46.3%) IBN100mg, 180 (45.5%) IBN150mg, 185 (46.7%)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Risedronate vs. placebo				
Boonen 2009[60] Men with OP	*Male/female:* 100% male *Race*: PBO, Caucasian, 88 (95%); Unknown 2 (2%); Asian, 1 (1%); Hispanic, 1 (1%); Indian, 1 (1%) RIS35mg/w, Caucasian, 181 (95%); Unknown, 7 (4%); Asian, 1 (1%); Hispanic, 1 (1%); Indian, 1 (1%) *Age*: PBO, 62 (11) RIS35mg/w, 60 (11) *Height; BMI:* PBO, 1.708m (0.74); 25 (4) RIS35mg/w, 1.727m (0.72); 25 (4)	None reported	Not reported	*Fractures:* not reported. *BMD:* PBO, Proximal femur (total proximal femur, femoral neck, femoral trochanter): 0.763 (0.106); T-score, -2.0 (0.7) RIS35mg/w, Proximal femur (total proximal femur, femoral neck, femoral trochanter): 0.768 (0.111); T-score, -2.0 (0.8)
Choo 2011[64] Men with androgen deprivation bone loss in non-metastatic prostate cancer	*Male/female:* 100% male *Race*: not reported *Age*: PBO, 66.8 RIS35mg/w, 66.2 *Height; weight; BMI:* not reported	*Comorbidities*: all were non-metastatic prostate cancer patients undergoing radiotherapy *Medications:* PBO, Median duration androgen ablation therapy, 2 years RIS35mg/w, Median duration androgen ablation therapy, 2.1 years	Not reported	Not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Cohen 1999[65] Men and women (≥1y PM) aged 18-85 years old on glucocorticoids	*Male/female:* PBO, 25/77 (32.5%) male RIS5mg/d, 27/76 (35.5%) male *Race*: not reported *Age*: PBO, 57.2 (14.7) RIS5mg/d, 66.2 (14.3) *Height; weight; BMI:* not reported	*Underlying disease requiring glucocorticoid treatment*: PBO, rheumatoid arthritis 31/77 (40.3%); polymyalgia rheumatic 19/77 (24.7%); systemic lupus erythematosus 10/77 (13.0%); giant cell ateriritis 5/77 (6.5%); vasculitis 8/77 (10.4%) RIS5mg/d, rheumatoid arthritis 27/76 (35.5%); polymyalgia rheumatic 25/76 (32.9%); systemic lupus erythematosus 12/76 (15.8%); giant cell ateriritis 5/76 (6.6%); vasculitis 3/76 (2.6%) *Medications:* All patients had begun taking moderate to high doses of glucocorticoids (≥7.5 mg/day mean daily dose of prednisone or prednisone equivalent) within the previous 3 months and were expected to continue treatment for another 12 months	Not reported	*Fractures*: PBO, Vertebral 22/77 (28.9%) RIS5mg/d, Vertebral 27/76 (36.0%) *FN BMD cm^3:* not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Fogelman 2000[68] (BMD-MN) Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 65 (6.7); 17 (9.4) RIS5mg/d, 65 (6.7); 18 (9.3) *Height; weight; BMI (estimated):* PBO, 157cm (6.7); 63kg (9.4); 25.6 RIS5mg/d, 158cm (5.3); 62kg (9.3); 24.8	*Comorbidities*: none reported *Previous osteoporotic medication:* PBO, 43/180 (24%) RIS5mg/d, 56/177 (32%)	Not reported	*Fractures*: PBO, Vertebral 52/180 (30.0%) RIS5mg/d, Vertebral 55/177 (32.0%) *FN BMD cm^3:* PBO, 0.636 (0.094) RIS5mg/d, 0.637 (0.093)
Hooper 2005[74] Early PM women with OP	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 52 (3.3); 3.9 (5.7) RIS5mg/d, 52 (3.1); 3.6 (4.8) *Height; weight; BMI* : not reported	None reported	Not reported	*Fractures*: PBO, vertebral 24/125 (19%) RIS5mg/d, vertebral 26/129 (20%) *FN BMD cm^3:* PBO, 0.78 (0.01) RIS5mg/d, 0.76 (0.01)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Harris 1999[72] (VERT-NA) (Extension Ste-Marie 2004[101]) Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 68 (7.2); 24 (10) RIS5mg/d, 69 (7.7); 24 (10.1) *Height; weight; BMI (estimated):* PBO, 159cm (6.9); 67kg (13.3); 26.5 RIS5mg/d, 158cm (6.8); 66.5kg (13.6); 26.6	None reported	Not reported	*Fractures*: PBO, vertebral 639/820 (79%) RIS5mg/d, vertebral 645/821 (80%) *FN BMD cm^3:* PBO, 0.602 (0.102) RIS5mg/d, 0.593 (0.105)
Reginster 2000[87] (VERT-MN) (Extension Sorensen 2003[102]) Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 71 (7.0); 25 (8.7) RIS5mg/d, 71 (7.0); 25 (8.6) *Height:* PBO, 155.5 (7.1) RIS5mg/d, 154.9 (7.3)	None reported	Not reported	*Median (range) no. vertebral fractures*: PBO, 3 (0-13) RIS5mg/d, 4 (0-13) *FN BMD cm^3:* PBO, 0.576 (0.093) RIS5mg/d, 0.573 (0.098)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Leung 2005[77] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: PBO, 67 (6); 15.1 (2.2) RIS5mg/d, 67 (6); 15.5 (1.6) *Height; weight; BMI (estimated):* PBO, 1.5m (0.05); 48.6kg (8); 21.6 RIS5mg/d, 1.5m (0.05); 49.5kg (6.3); 22.0	None reported	Not reported	*Fractures*: not reported *FN BMD cm^3:* PBO, 0.50 (0.08) RIS5mg/d, BMD 0.52 (0.05 *FN BMD T score:* PBO, -2.72 (0.85) RIS5mg/d, BMD -2.55 (0.58)
McClung 2001[80] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: All 70-79 year old 74 (3); 28 (8) All ≥80 years 83 (3); 37 (7) *Height; weight; BMI:* not reported	None reported	Not reported	*Vertebral fractures*: PBO 70-79 year old, 562/1821 (39%) PBO ≥80 years, 394/1313 (45%) RIS2.5+5mg groups 70-79 year old, 1100/3624 (38%) RIS2.5+5mg groups ≥80 years, 743/7543 (44%) *FN BMD cm^3:*not reported *FN BMD T score:* PBO 70-79 year old, -3.7 (0.6) RIS2.5+5mg groups 70-79 year old, -3.7 (0.6)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Reid 2000[88] Men and women taking glucocorticoids for ≥6 months.	*Male/female:* PBO, 36/96 (38%) male RIS5mg/d, 36/100 (36%) male *Race*: not reported *Age*: PBO, 59 (12) RIS5mg/d, 59 (12) *Height; weight; BMI:* not reported	*Underlying disease requiring glucocorticoid treatment:* PBO, rheumatoid arthritis 31/96 (41%); asthma 19/96 (20%); polymyalgia rheumatic 11/96 (12%); systemic lupus erythematosus 5/96 (5%); temporal arteritis 7/96 (7%); vasculitis 3/96 (3%); COPD 1/96 (1%); polymyositis 4/96 (4%); chronic intestinal lung disease 2/96 (2%); other 5/96 (5%) RIS5mg/d, rheumatoid arthritis 44/100 (44%); asthma 18/100 (18%); polymyalgia rheumatic 13/100 (13%); systemic lupus erythematosus 8/100 (8%); temporal arteritis 4/100 (4%); vasculitis 4/100 (4%); COPD 3/100 (3%); polymyositis 2/100 (2%); chronic intestinal lung disease 1/100 (1%); other 3/100 (3%) *Medications:* All patients had been receiving oral glucocorticoids (mean daily dose of prednisone ≥ 7.5 mg, or equivalent) for at least 6 months.	Not reported	*Fractures*: PBO, Vertebral 35/96 (37%) RIS5mg/d, Vertebral 34/100 (34%) *FN BMD cm^3:* not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Ringe 2006[91] (Extension Ringe 2009 [103]) Men with OP	*Male/female:* 100% male *Race*: not reported *Age*: PBO, 58.0 (10.3) RIS5mg/d, 55.8 (10.5) *Height; weight; BMI (estimated):* PBO, 174.2cm (6.2); 73.1kg (9.6); 24.1 RIS5mg/d, 174.7cm (7.0); 76.2kg (13.5); 25	None reported	Not reported	*≥1 vertebral fracture*: PBO, 81/158 (51.3%) RIS5mg/d, 84/158 (53.2%) *FN BMD cm^3:* not reported *FN BMD T-score:* PBO, -2.59 RIS5mg/d, -2.45
Taxel 2010[97] Men aged >55 years and within a month of receiving an initial injection of ADT for prostate cancer	*Male/female:* 100% male *Race*: not reported *Age*: PBO, 70 RIS35mg/w, 72 *BMI:* PBO, 29.3 (5.4) RIS35mg/w, 28.0 (2.9)	None reported	Not reported	*Fractures:* not reported *FN BMD cm^3:* PBO, 0.98 (0.16) RIS35mg/w, 0.95 (0.91) *FN BMD T-score:* PBO, -0.67 (1.24) RIS35mg/w, -0.95 (0.91)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Zoledronate vs. placebo				
Black 2007[58] (HORIZON-PFT) (HRQoL, Adachi 2011[105]) Women with PMO	*Male/female:* 100% female *Race*: PBO, Caucasian, 965 (90.9); Hispanic, 70 (6.6%); Black, 12 (1.1%); Other, 15 (1.4%) ZOL5mg/y, Caucasian, 973 (91.4%); Hispanic, 70 (6.6%); Black, 6 (0.6%); Other, 16 (1.5%) *Age*: PBO, 73.0 (5.40) ZOL5mg/y, 73.1 (5.34) *BMI:* PBO, 24.8 (4.5) ZOL5mg/y, 24.7 (4.4)	None reported	Not reported	*No. vertebral fractures:* PBO, 0, 1383 (35.8); 1, 1076 (27.9); ≥2, 1401 (36.3) ZOL5mg/y, 0, 1457 (37.6); 1, 1093 (28.2); ≥2, 1323 (34.1) *FN BMD cm^3:* PBO, 0.53 (0.064) ZOL5mg/y, 0.53 (0.062) *No. with FN BMD T-score:* PBO, < -2.5, 2734 (70.8%); -2.5 to -1.5, 1073 (27.8%); > -1.5, 38 (1.0%) ZOL5mg/y, < -2.5, 2814 (72.6%); -2.5 to -1.5, 1002 (25.9%); > -1.5, 35 (0.9%)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Lyles 2007[79] (HORIZON-RFT) Men and women 50 years of age or older within 90 days after surgical repair of a hip fracture	*Male/female:* PBO, 260/1062 (24.5%) male ZOL5mg/y, 248/1065 (23.3%) male *Race*: PBO, Caucasian 965 (90.9); Hispanic, 70 (6.6%); Black, 12 (1.1%); Other, 15 (1.4%) ZOL5mg/y, Caucasian, 973 (91.4%); Hispanic, 70 (6.6%); Black, 6 (0.6%); Other, 16 (1.5%) *Age*: PBO, 74.6 (9.86) ZOL5mg/y, 74.4 (9.48) *BMI:* PBO, 24.8 (4.5) ZOL5mg/y, 24.7 (4.4)	*Comorbidities*: The most common coexisting medical conditions at baseline were hypertension, coronary artery disease, osteoarthritis, previous stroke, depression, and diabetes mellitus n/N (%) not reported. Active tachyarrhythmia was present in 5.8% of patients in the ZOL group and in 7.5% of patients in the PBO group	Not reported	*Fractures:* All patients who were enrolled in the trial had undergone repair of a hip fracture *FN BMD cm^3:* PBO, 0.65 (0.122) ZOL5mg/y, 0.65 (0.127) *FN BMD T score:* PBO, -2.5 or less, 437 (41.1%); More than -2.5 to -1.5, 375 (35.3%); More than -1.5, 121 (11.4%) Missing data: 129 (12.1%) ZOL5mg/y, -2.5 or less, 451 (42.3%); More than -2.5 to -1.5, 360 (33.8%); More than -1.5, 123 (11.5%) Missing data: 131 (12.3%)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Boonen 2012[61] Men with OP	*Male/female:* 100% male *Race*: PBO, Caucasian 578 (94.6); Black 3 (0.5); Asian 0 (0.0); Other 30 (4.9) ZOL5mg/y, Caucasian555 (94.4); Black 5 (0.9); Asian 2 (0.3); Other 26 (4.4) 30 (4.9) *Age median (range)*: PBO, 66 (50 to 85) ZOL5mg/y, 66 (50 to 85) *Height; weight; BMI:* not reported	*Comorbidities*: none reported *Osteoporosis medications used before the first infusion in the study:* PBO, Bisphosphonates, 7 (1.1%); Calcitonin, 1 (0.2%) ZOL5mg/y, Bisphosphonates, 8 (1.4%); Calcitonin, 4 (0.7%)	Not reported	*No. of vertebral fractures:* PBO, 0, 409 (66.9%) ; 1, 135 (22.1); ≥2, 66 (10.8) ZOL5mg/y, 0, 404 (68.7); 1, 135 (22.1); ≥2, 66 (10.8) *FN BMD cm^3:* not reported *FN BMD T score:* PBO, -2.44 (0.685) ZOL5mg/y, -2.23 (0.677)
McClung 2009[81] Women with PMO	*Male/female:* 100% female *Race*: PBO, Caucasian 186 (92.1), other 16 (8) Caucasian 184 (92.9), other 12 (6.7) *Age; yrs. since menopause*: PBO, 60.5 (8.0); 11.4 (9.5) ZOL5mg/y, 59.6 (8.0); 11.5 (10.1) *BMI:* PBO, 27.2 (5.5) ZOL5mg/y, 27.3 (5.8)	None reported	Not reported	*Fractures:* not reported *FN BMD cm^3:* PBO, 0.69 (0.07) ZOL5mg/y, 0.69 (0.08) *FN BMD T score:* PBO, -1.47 (0.63) ZOL5mg/y, -1.40 (0.56)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Head-to-head – Alendronate vs. Ibandronate				
Miller 2008[83] (MOTION) Women with PMO	*Male/female:* 100% female *Race*: ALN70mg/w, Caucasian, 705/873 (80.8%) IBN150mg/m, Caucasian, 739/887 (83.3%) *Age; yrs. since menopause*: ALN70mg/w, 65.6; 18.2 IBN150mg/m, 65.6; 18.5 *Height; weight; BMI (estimated):* ALN70mg/w, 155cm; 62.28kg; 25.9 IBN150mg/m, 154.6cm; 62.01kg; 25.9	None reported	Not reported	*Previous fractures (not described):* ALN70mg/w, 38.2%; since age 45, 31.6% IBN150mg/m, 39%; since age 45, 32.5% *FN BMD/T score:* not reported
Head-to-head – Alendronate vs. Risedronate				
Atmaca 2006[56] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age; yrs. since menopause*: RIS5mg/d, 65.7 (4); 15 (4.7) ALN10mg/d, 66.3 (3.8); 15.9 (4.9) *Height; weight; BMI:* not reported	None reported	Not reported	*Fractures:* not reported *FN BMD cm^3:* RIS5mg/d, 0.603 (0.06) ALN10mg/d, 0.601 (0.06) *FN BMD T score*: not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Muscoso 2004[84] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age*: RIS5mg/d, 71 (8) ALN10mg/d, 66 (9) *Height; weight; BMI:* not reported	None reported	Not reported	Not reported
Sarioglu 2006[94] Women with PMO	*Male/female:* 100% female *Race*: not reported *Age*: RIS5mg/d, 60.3 (7.1) ALN10mg/d, 57.3 (6.6) *Height; weight; BMI:* RIS5mg/d, 60.3 (7.1); 14.7 (2.7); 27.7 (3.0) ALN10mg/d, 57.3 (6.6); 12.1 (2.4); 27.0 (4.5)	None reported	Not reported	*Fractures:* RIS5mg/d, 2 had vertebral fractures ALN10mg/d, 3 had vertebral fractures *FN BMD cm^3:* RIS5mg/d, 0.764 (0.129) ALN10mg/d, 0.784 (0.096) *FN BMD T score*: not reported

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Rosen 2005[92] (FACT) (Extension Bonnick 2005[106]) Women with PMO	*Male/female:* 100% female *Race*: ALN70mg/w, Caucasian 491/520 (94.4%); black 8/520 (1.5%); Asian 7/520 (1.3%); other 14/520 (2.8%) RIS35mg/w, Caucasian 512/533 (96.1%); black 2/533 (0.4%); Asian 8/533 (1.5%); other 11/533 (2.0%) *Age; yrs. since menopause*: ALN70mg/w, 64.2 (9.9); 18.3 (12.3) RIS35mg/w, 64.8 (9.7); 18.7 (11.6) *BMI:* ALN70mg/w, 25.2 (4.7) RIS35mg/w, 25.5 (4.5)	None reported	Not reported	*Fracture history of hip, spine, or wrist after age 45:* ALN70mg/w, 60/520 (11.5%) RIS35mg/w, 66/533 (12.4%) *FN BMD cm^3: n*ot reported *FN BMD T-Score:* ALN70mg/w, -2.12 (0.66) RIS35mg/w, -2.16 (0.67)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Reid 2006[89] (FACTS) (Extension Reid 2008[107]) Women with PMO.	*Male/female:* 100% female *Race*: ALN70mg/w, Caucasian 371/468 (79.3%); Hispanic 39/468 (8.3%); Asian 35/468 (7.5%); other 23/468 (4.9%) RIS35mg/w, Caucasian 364/468 (77.8%); Hispanic 43/468 (9.2%); Asian 36/468 (7.7%); other 25/468 (5.3%) *Age; yrs. since menopause*: ALN70mg/w, 64.3 (8.1); 16.9 (9.5) RIS35mg/w, 63.9 (8.3); 16.8 (9.4) *BMI:* ALN70mg/w, 25.2 (4.7) RIS35mg/w, 25.5 (4.5)	None reported	*Family history of osteoporosis:* ALN70mg/w, 152 (43.1%) RIS35mg/w, 139 (39.0%)	*Fracture history (not described):* ALN70mg/w, 166 (35.5%) RIS35mg/w, 149 (31.8%) *FN BMD cm^3:* not reported *FN BMD T-Score:* ALN70mg/w, -2.06 (0.76) RIS35mg/w, -2.17 (0.75)

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Head-to-head – Zoledronate vs. Alendronate				
Hadji 2012[71] Hadji 2010[108] (ROSE) Women with PMO	*Male/female:* 100% female *Race*: ZOL5mg/y, Caucasian 403 (98.8%) 188 (98.4%); Black 1 (0.2%) 1 (0.5%); Asian 1 (0.2%) 0 (0%); Other 2 (0.5%); Missing 1 (0.2%) ALN70mg/w, Caucasian 188 (98.4%); Black 1 (0.5%); Asian 0 (0%); Other 2 (1.0%); Missing 0 (0%) *Age*: ZOL5mg/y, 67.6 (8.05) ALN70mg/w, 68.1 (7.86) *BMI:* ZOL5mg/y, 26.1 (4.12) ALN70mg/w, 26.3 (4.0)	None reported	*Current and previous smokers:* ZOL5mg/y, 97/408 (23.8%) ALN70mg/w, 40/194 (20.9%)	*Fractures (not described):* ZOL5mg/y, 134/408 (32.8%) ALN70mg/w, 65/194 (34.0%) *FN BMD cm^3:* not reported ZOL5mg/y, n=408 ALN70mg/w, n=196 *FN BMD T-Score:* ZOL5mg/y, n=408 ALN70mg/w, n=196

Trial and population	n/N (%) male, Mean (SD): age; years since menopause; height/weight/BMI	Comorbidities; associated medication	Smoking; alcohol use; history of: steroid use, falls, history of low BMI, family hip fracture/history of OP	n/N (%) baseline/history factures; mean (SD) FN BMD/T score
Head-to-head – Zoledronate vs. Risedronate				
Reid 2009[90] (HORIZON) Men and women taking glucocorticoids ≥3mo and <3mo	*Male/female:* ZOL5mg/y treatment, 87 (32%) male; prevention, 44 (31%) male RIS5mg/d treatment, 90 (33%) male; prevention, 44 (31%) male *Race*: not reported *Age*: ZOL5mg/y treatment, 53.2 (14.0); prevention, 56.3 (15.4) RIS5mg/d - treatment, 52.7 (13.7); prevention, 58.1 (14.7) *Height; weight; BMI:* not reported	*Medical disorders requiring glucocorticoid use*: ZOL5mg/y treatment, Rheumatoid arthritis 119 (44%), Polymyalgia 13 (5%), Lupus 41 (15%), Asthma 23 (8%) ZOL5mg/y prevention, Rheumatoid arthritis 56 (39%), Polymyalgia 29 (20%), Lupus 10 (7%), Asthma 7 (5%) RIS5mg/d treatment, Rheumatoid arthritis 114 (42%), Polymyalgia 13 (5%), Lupus 44 (16%), Asthma 20 (7%) RIS5mg/d prevention, Rheumatoid arthritis 53 (37%), Polymyalgia 29 (20%), Lupus 15 (10%), Asthma 4 (3%)	Not reported	*Fractures:* not reported *FN BMD/T score*: not reported

ALN, alendronate; BMD, bone mineral density; BMI, body mass index; FN, femoral neck; HRQoL, Health-related quality of life; IBN, ibandronate; mg/d, milligrams per day; mg/m, milligrams per month; mg/y, milligrams per year; OP, osteoporosis; PBO, placebo; PM, postmenopausal; PMO, postmenopausal osteoporosis; RCT, randomised controlled trial; RIS, risedronate; SD, standard deviation; ZOL, zoledronate

Alendronate

Alendronate was evaluated against placebo in 17 RCTs reported across 19 publications.[55,57,59,62,63,66,67,69,70,73,75,78,85,86,93,95,96,99,100] Two RCTs did not include a placebo comparison, but evaluated alendronate combined with calcium against calcium alone.[67,73]

RCT location and funding

Four RCTs were multicentre RCTs undertaken in the USA.(FIT I, Black *et al.*, 1996;[57] Chesnut *et al.*, 1995;[63] FIT II, Cummings *et al.*, 1998;[66]; Greenspan *et al.*, 2002[69]) Six RCTs were international multicentre RCTs.(Adachi *et al.*, 2001;[100] Liberman *et al.*, 1995;[78] FOSIT, Pols *et al.*, 1999;[86] Saag *et al.*, 1998;[93] Orwoll *et al.*, 2000;[85] Smith *et al.*, 2004[96]) One multicentre RCT was undertaken in Italy.(Adami *et al.*, 1995[55]) One multicentre RCT was undertaken in Canada.(CORAL, Klotz *et al.*, 2013[75]) Single centre RCTs were undertaken in Italy,(Carfora *et al.*, 1998[62]) Turkey(Dursun *et al.*, 2001[67]) and Jordan.(Shilbayeh *et al.*, 2004[95]) The countries and number of participating centres was unclear for one RCT,(Bone *et al.*, 2000[59]) and the number of participating centres was unclear for one RCT undertaken in China.(Ho *et al.*, 2005[73]) RCT sponsor details were not reported for four RCTs.(Adami *et al.*, 1995;[55] Carfora *et al.*, 1998;[62] Dursun *et al.*, 2001;[67] Shilbayeh *et al.*, 2004[95]) Total numbers of participants randomised ranged from 63(Shilbayeh *et al.*, 2004[95]) to 4,432.(FIT II, Cummings *et al.*, 1998[66])

Populations recruited and treatment dosage

Fourteen RCTs recruited postmenopausal women and evaluated alendronate 10 milligrams (mg) per day.(Adami *et al.*, 1995;[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Bone *et al.*, 2000;[59] Carfora *et al.*, 1998;[62] Chesnut *et al.*, 1995;[63] Dursun *et al.*, 2001;[67] Greenspan *et al.*, 2002;[69] Greenspan *et al.*, 2003;[70] Ho *et al.*, 2005;[73]; Liberman *et al.*, 1995;[78] FOSIT, Pols *et al.*, 1999;[86] Shilbayeh *et al.*, 2004;[95] Saag *et al.*, 1998[93]) Two of these RCTs also included an evaluation of other doses of alendronate not currently licensed.(Adachi *et al.*, 2001;[100] Liberman *et al.*, 1995[78,93]) Two of the RCTs in postmenopausal women reported that participants were switched from a 5 mg daily dose of alendronate to 10 mg per day after 24 months spending the remaining 12 months of the RCT on 10 mg per day.(FIT I, black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998[66]) One RCT evaluated alendronate 10 mg per day in men with osteoporosis,(Orwoll *et al.*, 2000[85]) one RCT evaluated 10 mg per day in men and women (51% male) with airways disease,(Smith *et al.*, 2004[96]) and one RCT evaluated 70 mg per week in men with androgen deprivation therapy (ADT) bone loss in non-metastatic prostate cancer.(CORAL, Klotz *et al.*, 2013[75]) One RCT in men and women (37.4% male) with underlying diseases requiring long-term oral glucocorticoid therapy, evaluated alendronate 5 mg or 10 mg per day (two active treatment groups), reporting fracture

outcomes for the 5 mg and 10 mg group participants combined (data not used in the analysis for this assessment report).(Saag *et al.*, 1998[93])

Adjuvant therapy

Adjuvant treatment in the form of calcium alone or in combination with vitamin D was reported for all RCTs. The doses varied across the RCTs (Table 4).

BMD of recruited participants

Inclusion criteria varied across the RCTs in terms of baseline BMD and T-scores (skeletal site and cut-off). Seven RCTs (Adami *et al.*, 1995;[55] Bone *et al.*, 2000;[59] Carfora *et al.*, 1998;[62] Ho *et al.*, 2005;[73] Liberman *et al.*, 1995;[78] FOSIT, Pols *et al.*, 1999;[86] Shilbayeh *et al.*, 2004[95]) reported inclusion criteria that would identify women with osteoporosis according to the current WHO definition.[2] Two RCTs recruited women aged 55 to 81 years with a femoral neck BMD ≤2 SDs below normal young adult,(FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998[66]) an additional inclusion criterion for one of these RCTs being women with at least one vertebral fracture.(FIT I, Black *et al.*, 1996[57]) One RCT recruited women aged 42 to 75 years with lumbar spine BMD approximately 2 SDs below young normal,(Chesnut *et al.*, 1995[63]) and another RCT recruited women with BMD 2 standard deviations (SDs) or more below young adult mean at either lumbar spine or femoral neck.(Dursun *et al.*, 2001[67]) One RCT recruited ambulatory women in long-term care ≥65 years, with lumbar spine or total hip BMD T-score of ≤-2.0 SD. One RCT recruited community-dwelling women aged 65 or older.(Greenspan *et al.*, 2000[69]) Femoral neck above mean peak was an exclusion criterion for one RCT.(Greenspan *et al.*, 2003[70]) One RCT recruited men and women with underlying diseases requiring long-term oral glucocorticoid therapy irrespective of baseline BMD.(Saag *et al.*, 1998[93]) One RCT recruited men with femoral neck and lumbar T-scores <2 SDs and <1 SD below normal young men, or femoral neck BMD ≤1SD below normal young plus vertebral deformity or fracture.(Orwoll *et al.*, 2000[85]) The RCT in men and women with airways disease only included participants with a T-score <-2.5, or Z-score <-1.0 at hip or lumbar spine.(Smith *et al.*, 2004[96]) The RCT in men with ADT bone loss reported 38% of all participants had osteopenia and 7% had osteoporosis.(CORAL, Klotz *et al.*, 2013[75])

Age, race, years post menopause, BMI and smoking status

The mean age of participants was in the sixth decade (between 51 and 60 years) in two RCTs.(Adami *et al.*, 1995;[55] Saag *et al.*, 1998[93]). One RCT did not report mean age, but recruited women age 44 to 73.(Carfora *et al.*, 1998[62]) Another RCT not reporting mean age included participants >60 years to <70 years.(Smith *et al.*, 2004[96]) In one RCT mean age of all included participants was 73.6 years.(CORAL, Klotz *et al.*, 2013[75]) In all other RCTs the

mean age of included participants was in the seventh decade (between 61 and 70 years). Seven RCTs in women reported on the number of years since menopause.(Adami *et al.*, 1995;[55] Chesnut *et al.*, 1995;[63] Bone *et al.*, 2000;[59] Dursun *et al.*, 2001;[67] Ho *et al.*, 2005;[73] FOSIT, Pols *et al.*, 1999;[86] Shilbayeh *et al.*, 2004[95] The mean number of years since menopause ranged from 10 to 15 years across all of these RCTs with the exception of one RCT recruiting women after hysterectomy in which the mean number of years since menopause was 22.(Bone *et al.*, 2000[59]) Body mass index (BMI) was available for twelve RCTs.(Adami *et al.*, 1995;[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Chesnut *et al.*, 1995;[63] Dursun *et al.*, 2001;[67] Greenspan *et al.*, 2003;[70] Ho *et al.*, 2005;[73] Liberman *et al.*, 1995;[78] Orwoll *et al.*, 2000;[85] FOSIT, Pols *et al.*, 1999;[86] Shilbayeh *et al.*, 2004;[95] Saag *et al.*, 1998[93]) Across these RCTs, all mean BMI values were greater than 18.5 kg/m^2. In one RCT mean BMI was greater than 30 kg/m^2.(Shilbayeh *et al.*, 2004[95]) Race of included participants was reported by eight RCTs.(FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Bone *et al.*, 2000;[59] Chesnut *et al.*, 1995;[63] Greenspan *et al.*, 2002;[69] Ho *et al.*, 2005;[73] FOSIT, Pols *et al.*, 1999;[86] Saag *et al.*, 1998[93]) One of these recruited 100% East Asian women.(Ho *et al.*, 2005[73]) Across the other RCTs the proportion of Caucasian participants was ≥90%. Smoking status was reported by five RCTs,(Adami *et al.*, 1995[55] Black *et al.*, 1996;[57] Cummings *et al.*, 1998;[66] Smith *et al.*, 2004;[96] CORAL, Klotz *et al.*, 2013;[75] four RCTs reporting ≥10% of included participants were current smokers.(Adami *et al.*, 1995[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Smith *et al.*, 2004[96]) Mean smoking years of 26.2 and mean packs per day of 0.98 was reported by one RCT.(CORAL, Klotz *et al.*, 2013[75])

Fractures at baseline

The presence of fractures or fracture history at baseline was reported by nine RCTs.(Adami *et al.*, 1995;[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Greenspan et al, 2002;[69] Greenspan *et al.*, 2003;[70] Ho et al, 2005;[73] Liberman et al, 1995;[78] Orwoll *et al.*, 2000;[85] CIRAL, Klotz *et al.*, 2013[75]) One RCT reported that 5% of all participants had vertebral fractures,(Adami *et al.*, 1995[55]) one RCT reported that 37% had vertebral fractures(Ho *et al.*, 2005[73]) and one RCT reported that 41.9% had vertebral fractures.(Orwoll at el., 2000[85]) One RCT reported that 64% of participants had at least one vertebral fracture and that 14% had three or more vertebral fractures.(FIT I, Black *et al.*, 1996[57]) One RCT reported that 21% of participants had vertebral fractures and 5% had non-vertebral fractures at baseline.(Liberman *et al.*, 1995[78]) Fifty-five percent (55%) of participants in one RCT had a history of fracture.(Greenspan *et al.*, 2002[69]) One RCT reported that of the 47% who reported prior fracture, 1% had had a history of hip or vertebral fracture.(CORAL, Klotz *et al.*, 2013[75]) One RCT reported that 36% had experienced fractures since age 50(Greenspan *et al.*, 2003[70])

and one RCT reported that 35% had experienced fractures since age 45.(FIT II, Cummings *et al.*, 1998[66])

Assessment of treatment compliance

Compliance with treatment in the form of a pill count was assessed by three RCTs.(Adami *et al.*, 1995;[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66])

Follow-up and participants completing RCTs

Final follow-up was 12 months in six RCTs,(Dursun *et al.*, 2001;[67] Ho *et al.*, 2005;[73] FOSIT, Pols *et al.*, 1999;[86] Shilbayeh *et al.*, 2004;[95] Smith *et al.*, 2004;[96] CORAL, Klotz *et al.*, 2013;[75]) 24 months in five RCTs,(Adami *et al.*, 1995;[55] Bone *et al.*, 2000;[59] Chesnut *et al.*, 1995;[63] Greenspan *et al.*, 2002;[69] Orwoll *et al.*, 2000[85]) 30 months in one trial,(Carfora *et al.*, 1998[62]) 36 months in three RCTs,(FIT I, Black *et al.*, 1996;[57] Greenspan *et al.*, 2003;[70] Liberman *et al.*, 1995[78]) and 48 months in one RCT.(FIT II, Cummings *et al.*, 1998[66]) One RCT reported an initial follow-up of 12-months(Saag *et al.*, 1998[93]) with an extension to 24-months.(Adachi *et al.*, 2000[100])

The number of participants completing was not reported for two RCTs(Carfora *et al.*, 1998;[62]) Greenspan *et al.*, 2002[69]) (Table 6). Overall completion rates of ≥90% were reported by seven RCTs(Adami *et al.*, 1995;[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Greenspan *et al.*, 2003;[70] Ho *et al.*, 2005;[73] CORAL, Klotz *et al.*, 2013[75]) (Table 6). The highest rate of participant withdrawal was reported by Shilbayeh *et al.* (2004), [95] with 40% of participants withdrawing overall (Table 6).

Post-treatment fracture assessment

Fractures were not assessed as an outcome in four RCTs.(Adami *et al.*, 1995[55] Chesnut *et al.*, 1995;[63] Ho *et al.*, 2005;[73] Shilbayeh *et al.*, 2004[95]) Across the RCTs assessing fractures, classification of the fracture and the method of assessment was diverse (Table 4). Five RCTs recorded fractures as adverse events,(Bone *et al.*, 2000;[59] Greenspan *et al.*, 2003;[70] Greenspan *et al.*, 2002;[69] FOSIT, Pols *et al.*, 1999;[86] CORAL, Klotz *et al.*, 2013[75]) four of which did not report details of the assessment method.(Bone *et al.*, 2000;[59] Greenspan *et al.*, 2002;[69] Greenspan *et al.*, 2003;[70] CORAL, Klotz *et al.*, 2013[75]) Vertebral fractures were assessed by seven RCTs.(FIT II, Black *et al.*, 1996[57] FIT II, Cummings *et al.*, 1998;[66] Carfora *et al.*, 1998;[62] Dursun *et al.*, 2001;[67] Liberman *et al.*, 1995;[78] Orwoll *et al.*, 2000;[85] Saag *et al.*, 1998[93]) All seven RCTs reported that vertebral fractures where assessed radiographically. One of the RCTs also assessed clinical fractures (non-spine clinical fractures, hip fractures, wrist fractures, and clinical vertebral fractures; and other clinical fractures) reported by

participants and confirmed by radiograph,(FIT I, Black *et al.*, 1996[57]) and one RCT reported that clinical fractures (clinical vertebral, hip or wrist) were assessed by participant self-reports confirmed by radiograph.(FIT II, Cummings *et al.*, 1998[66]). One RCT reported that non-vertebral fractures were assessed from patient reporting, confirmed by radiograph (Orwoll *et al.*, 2000[85])

Post-treatment femoral neck BMD assessment

Femoral neck BMD assessment was reported by all but one of the RCTs.(Carfora *et al.*, 1998[62]) Where assessed, BMD assessment was by DXA. With the exception of one RCT that did not report on DXA manufacturer,(Dursun *et al.*, 2001[67]) all assessed BMD using DXA Hologic machines.

Ibandronate

Ibandronate 150 mg per month was evaluated against placebo in two RCTs (ARIBON, Lester *et al.*, 2008;[76] McClung *et al.*, 2009[82]) and ibandronate 2.5 mg per day was evaluated against placebo in one RCT.(BONE, Chesnut *et al.*, 2004[45]) This RCT also evaluated ibandronate 20mg every other day for 12 doses per month (not current licensed dose). One RCT evaluated ibandronate 2.5 mg per day, 2 mg i.v. every two months (not current licenced dose) and 3 mg i.v. every three months (current licenced dose).(DIVA, Delmas *et al.*, 2006[49]). One RCT evaluated ibandronate 2.5 mg per day, 50 mg twice per month, 100 mg per month and 150 mg per month (current licensed dose).(MOBILE, Miller *et al.* 2005[47])

RCT location and funding

All five RCTs were multicentre RCTs, one undertaken in the UK,(ARIBON, Lester *et al.*, 2008[76]) one in the USA,(McClung *et al.*, 2009[82]) one in Europe and the USA,(BONE, Chesnut *et al.*, 2004[45]) one in the USA, Canada, Mexico, Europe, Australia and South Africa,(DIVA, Delmas *et al.*, 2006[49]) and one in the USA, Canada, Europe, Australia, South Africa, Mexico, and Brazil.(MOBILE, Miller *et al.* 2005[47]) RCT sponsor details were reported for all five RCTs. Total numbers of participants randomised ranged from 50(ARIBON, Lester *et al.*, 2008[76]) to 2,946.(BONE, Chesnut *et al.*, 2004[45])

Populations recruited and treatment dosage

All of the RCTs recruited postmenopausal women, one of which recruited postmenopausal women with a histologically confirmed diagnosis of oestrogen receptor-positive breast cancer.(ARIBON, Lester *et al.*, 2008[76])

Adjuvant therapy

Adjuvant treatment in the form of calcium 500 mg per day and vitamin D 400IU per day was prescribed across all five RCTs.

BMD of recruited participants

Four of the RCTs(McClung *et al.*, 2009;[82] BONE, Chesnut *et al.*, 2004;[45] DIVA, Delmas *et al.*, 2006;[49] MOBILE, Miller *et al.* 2005[47]) reported inclusion criteria that would identify women with osteoporosis according to the current WHO definition.[2] The RCT in women with breast cancer recruited women classified as osteopenic (T scores of >-2.5 and <-1.0 either at the lumbar spine or total hip).(ARIBON, Lester *et al.*, 2008[76])

Age, race, years post menopause and BMI

Four RCTs recruited participants with a mean age in the seventh decade (between 61 and 70).(BONE, Chesnut *et al.*, 2004;[45] ARIBON, Lester *et al.*, 2008;[76] DIVA, Delmas *et al.*, 2006;[49] MOBILE, Miller *et al.* 2005[47]) Mean age in the other RCT was 53.6 years.(McClung *et al.*, 2009[82]) The mean number of years since menopause in one RCT recruiting early postmenopausal women was 4.2.(McClung et la., 2009[82]) Mean years since menopause was 20.8 in one trial,(BONE, Chesnut *et al.*, 2004[45]) 18.7 in one RCT.(DIVA, Delmas *et al.*, 2006[49]) and 18.6 in one RCT.(MOBILE, Miller *et al.* 2005[47]) One RCT did not report on years since menopause.(ARIBON, Lester *et al.*, 2008[76]) Mean BMI values were greater than 18.5 kg/m^2 in all RCTs. One RCT reported median BMI <30 kg/m^2 in both placebo and ibandronate participants.(ARIBON, Lester *et al.*, 2008[76]) Race of included participants was not reported by any RCT.

Fractures at baseline

The presence of fractures at baseline was reported by three RCTs, one in which 93% of participants had one vertebral fracture at baseline and 43% had two,(BONE, Chesnut *et al.*, 2004[45]) one in which 42.1% had fractures at baseline,(DIVA, Delmas *et al.*, 2006[49]) and one in which 4.9% had fractures at baseline.(MOBILE, Miller *et al.* 2005[47])

Assessment of treatment compliance

Compliance with treatment in the form of a pill count was assessed by one RCT.(ARIBON, Lester *et al.*, 2008[76])

Follow-up and participants completing RCTs

Final follow-up was 12 months in two RCTs,(McClung et la., 2009;[82] MOBILE, Miller *et al.* 2005[47]) 24 months in two RCTs(ARIBON, Lester *et al.*, 2008;[76] DIVA, Delmas *et al.*, 2006[49])

and 36 months in one RCT.(BONE, Chesnut *et al.*, 2004[45]) None of the RCTs reported a completion rate of ≥90% (Table 6).

The highest rate of participant withdrawal was reported by the BONE trial,(Chesnut *et al.*, 2004[45]) with 34% participants withdrawing overall (Table 6).

Post-treatment fracture assessment

Fractures were recorded as adverse events, but the assessment method not reported in two RCTs.(ARIBON, Lester *et al.*, 2008;[76] MOBILE, Miller *et al.* 2005[47]) Two RCTs also assessed fractures as adverse events confirmed by radiograph.(McClung et la., 2009;[82] DIVA, Delmas *et al.*, 2006[49]) Vertebral fractures was the primary outcome confirmed by radiograph in one RCT.(BONE, Chesnut *et al.*, 2004[45])

Post-treatment femoral neck BMD assessment

Femoral neck BMD assessment was reported by all of the RCTs. BMD assessment was by DXA using Hologic or Lunar machines.

BMD and anti-fracture efficacy of ibandronate pivotal RCTs

One of the three placebo-controlled RCTs in ibandronate was the pivotal 3-year BONE study, in which the antifracture efficacy of daily oral ibandronate 2.5 mg and intermittent oral ibandronate 20 mg every other day for 12 doses every 3 months was assessed over 36 months.(BONE, Chesnut *et al.*, 2004[45]) The BONE RCT reported comparable vertebral antifracture efficacy of daily and intermittent administration, suggesting that ibandronate could be administered at intervals longer than daily or weekly. In a further non inferiority RCT 50mg then 50 mg (single doses on consecutive days), 100 and 150 mg doses of monthly ibandronate and daily 2.5 mg were evaluated in the MOBILE study.(MOBILE, Miller *et al.*, 2005[47]) The 150 mg dose produced the greatest gains in BMD compared with daily ibandronate (2.5 mg) at 2 years (lumbar spine BMD: 6.6 compared with 5.0%, respectively, $p< 0.001$). The DIVA study then compared the efficacy of two regimens of intermittent i.v. injections of ibandronate (2 mg every 2 months and 3 mg quarterly) with a regimen of daily oral ibandronate (2.5 mg), the latter of which has proven antifracture efficacy.(DIVA, Delmas *et al.*, 2006[49] At 2 years, the 2- and 3-monthly i.v. regimens produced improvements in spinal BMD (6.4% and 6.3%, respectively) that were superior to oral ibandronate (4.8%; $p<0.001$). The MOBILE and the DIVA studies confirmed a sustained efficacy of monthly oral and quarterly i.v. regimens respectively, over 5 years.(Bianchi *et al.*, 2009;[109] Felsenberg *et al.*, 2009[110])

Risedronate

Risedronate was evaluated against placebo in twelve RCTs reported across fifteen publications.[60,64,65,68,72,74,77,80,87,88,91,97,101-103]

RCT location and funding

Three RCTs were multicentre RCTs undertaken in the USA.(Cohen *et al.*, 1999;[65]; VERT-NA, Harris *et al.*, 1999;[72] McClung *et al.*, 2001[80]) One multicentre RCT was undertaken in Australia,(Hooper *et al.*, 2005[74]) one multicentre RCT was undertaken in China,(Leung *et al.*, 2005[77]) and one was undertaken in the UK.(Reid *et al.*, 2000[88]) Three RCTs were international multicentre RCTs.(Boonen *et al.*, 2009;[60] BMD-MN, Fogelman *et al.*, 2000;[68] VERT-MN, Reginster *et al.*, 2000[87]) One single centre RCT was undertaken in Germany.(Ringe *et al.*, 2006[91]) The number of participating centres was unclear for one RCT undertaken in Canada(Choo *et al.*, 2001[64]) and one RCT undertaken in USA.[97] With the exception of one RCT (two publications),[91,103] RCT sponsor details were reported for all included RCTs. Total numbers of participants randomised ranged from 40(Taxel *et al.*, 2010[97]) to 9,331.(McClung *et al.*, 2001[80])

Populations recruited and treatment dosage

Six RCTs recruited postmenopausal women and evaluated risedronate 5 mg per day. (BMD-MN, Fogelman *et al.*, 2000;[68] Hooper 2005 *et al.*, 2000;[74] VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000[87] Leung *et al.*, 2005;[77] McClung *et al.*, 2001[80]) Two of these RCTs also included an evaluation of other doses of risedronate not currently licensed,(BMD-MN, Fogelman *et al.*, 2000[68];McClung *et al.*, 2001[80]). Both of these RCTs reported fracture outcomes for 2.5 mg and 5 mg group participants combined (data not used in the analysis for this assessment report). One RCT evaluated risedronate 35 mg per week in men with osteoporosis, (Boonen *et al.*, 2009[60]) and one RCT evaluated 5 mg per day in men with osteoporosis.(Ringe *et al.*, 2006 [91]) Two RCTs evaluated 35 mg per week in men with non-metastatic prostate cancer patients receiving ADT.(Choo *et al.*, 2011[64];Taxel *et al.*, 2010[97]) Two RCTs in men and women (32.5% male[65] and 38% respectively[88]) receiving glucocorticoids, evaluated risedronate 5 mg per day.(Cohen *et al.*, 1999;[65] Reid *et al.*, 2000[88])

Adjuvant therapy

Adjuvant treatment in the form of calcium alone or in combination with vitamin D was reported for all RCTs. The doses varied across the RCTs (Table 4).

BMD of recruited participants

Inclusion criteria varied across the RCTs in terms of baseline BMD and T-scores (skeletal site and cut-off). Six RCTs(Boonen *et al.*, 2009[60] Leung *et al.*, 2005;[77] McClung *et al.*, 2001;[80] Ringe *et al.*, 2006;[91] Hooper 2005 *et al.*, 2000[74] BMD-MN, Fogelman *et al.*, 2000[68]) reported inclusion criteria that would identify men and women with osteoporosis according to the current WHO definition.[2] One RCT recruited women no older than 85 years with at least one vertebral fracture at baseline,(VERT-NA, Harris *et al.*, 1999[72]) and another RCT recruited women up to 85 years with at least two radiographically confirmed vertebral fractures.(VERT-MN, Reginster *et al.*, 2000[87]) Baseline BMD was not an inclusion criterion for either of the two RCTs in men and women receiving glucocorticoids(Cohen *et al.*, 1999;[65] Reid *et al.*, 2000[88]) or the two RCTs in men with prostate cancer receiving ADT.(Choo *et al.*, 2011;[64] Taxel *et al.*, 2010[97])

Age, race, years post menopause and BMI

The mean age of participants was in the sixth decade (between 51 and 60 years) in three RCTs.(Reid *et al.*, 2000;[88] Hooper 2005 *et al.*, 2000;[74] Ringe *et al.*, 2006 [91]) One RCT categorised women by age into two groups, those age 70 to 79 years, and those ≥80 years.(McClung *et al.*, 2001[80]) In two RCTs the mean age of all included participants was 71 years.(VERT-MN, Reginster *et al.*, 2000;[87] Taxel *et al.*, 2010[97]) In all other RCTs the mean age of included participants was in the seventh decade (between 61 and 70 years). Five RCTs in women reported on the number of years since menopause. (BMD-MN, Fogelman *et al.*, 2000;[68] VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000;[87] Leung *et al.*, 2005;[77] Hooper 2005 *et al.*, 2000[74]) The mean number of years since menopause ranged from 10 to 20 years across two of these RCTs,(BMD-MN, Fogelman *et al.*, 2000;[68] Leung *et al.*, 2005[77]) and 24 to 25 years in two RCTs.(VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000[87]) In the RCT categorising women by age into two groups, those age 70 to 79 years, and those ≥80 years, the mean age since menopause was 28 years and 37 years respectively.(McClung *et al.*, 2001[80]) The mean years since menopause in one RCT recruiting early postmenopausal women was 3.7 years.(Hooper 2005 *et al.*, 2000[74]) Body mass index (BMI) was available for five RCTs. (Boonen *et al.*, 2009;[60] BMD-MN, Fogelman *et al.*, 2000;[68] VERT-NA, Harris *et al.*, 1999;[72] Leung *et al.*, 2005;[77] Ringe *et al.*, 2006 [91]) Across these RCTs, all mean BMI values were greater than 18.5 kg/m^2. Race of included participants was reported by only one of the RCTs in which proportion of Caucasian participants was 95%.(Boonen *et al.*, 2009[60])

Fractures at baseline

The presence of fractures or fracture history at baseline was reported by eight RCTs.(Cohen *et al.*, 1999[65] BMD-MN, Fogelman *et al.*, 2000;[68] Hooper 2005 *et al.*, 2000;[74] VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000;[87] McClung *et al.*, 2001;[80] Reid *et al.*, 2000;[88] Ringe *et al.*, 2006[91]) Twenty percent (20%) of women in one RCT had vertebral fractures at baseline.(Hooper 2005 *et al.*, 2000[74]) In two RCTs circa 31% of all participants had vertebral fractures,(Cohen *et al.*, 1999;[65] BMD-MN, Fogelman *et al.*, 2000[68]) and in one RCT 35% had vertebral fractures.(Reid *et al.*, 2000[88]) One RCT reported that 42% had vertebral fractures(McClung *et al.*, 2001[80]) and one RCT reported that 52% had vertebral fractures.(Ringe *et al.*, 2006[91]) In one trial, 80% of all participants had vertebral fractures at baseline. (VERT-NA, Harris *et al.*, 1999[72]) One RCT reported the median number of vertebral fractures at baseline which was three in the placebo group and four in the risedronate group. (VERT-MN, Reginster *et al.*, 2000[87])

Assessment of treatment compliance

Compliance with treatment in the form of a pill count was assessed by two RCTs. (Boonen *et al.*, 2009[60]; Taxel *et al.*, 2010[97])

Follow-up and participants completing RCTs

Final follow-up was 12 months in three RCTs (Cohen *et al.*, 1999;[65] Leung *et al.*, 2005;[77] Reid *et al.*, 2000[88]) and 24 months in four RCTs.(Boonen *et al.*, 2009;[60] Choo *et al.*, 2011;[64] BMD-MN, Fogelman *et al.*, 2000;[68] Hooper 2005 *et al.*, 2000[74]) One RCT reported a final follow-up of six months(Taxel *et al.*, 2010[97]) and one RCT reported a follow-up of 36 months.(McClung *et al.*, 2001[80]) One RCT reported an initial follow-up of 12-months(Ringe *et al.*, 2006 [91]) with an extension to 24-months.(Ringe *et al.*, 2009[103]) Two RCTs reported an initial follow-up of 36-months(VERT-NA, Harris *et al.*, 1999[72] VERT-MN, Reginster *et al.*, 2000[87]) with an extension to 60 months.(Ste-Marie *et al.*, 2004;[101] Sorensen *et al.*, 2003[102])

The number of participants completing was not reported by three RCTs(Taxel *et al.*, 2010;[97] Choo *et al.*, 2011;[64] Leung *et al.*, 2005[77]) (Table 6). Only one RCT reported a completion rate of ≥90%(Ringe *et al.*, 2006 [91]) (Table 6). The highest rate of participant withdrawal was reported by McClung *et al.*, 2001[80] with 40% participants withdrawing overall (Table 6).

Post-treatment fracture assessment

Fractures were not assessed as an outcome in four RCTs.(Choo *et al.*, 2011;[64] Leung *et al.*, 2005;[77] Reid *et al.*, 2000;[88] Taxel *et al.*, 2010[97]) Across the RCTs assessing fractures, classification of the fracture and the method of assessment was diverse (Table 4). One

recorded clinical fractures (non-vertebral and vertebral fractures) confirmed by radiographs as adverse events.(Ste-Marie *et al.*, 2004[101]) This was an extension to a RCT in which vertebral fractures were the primary outcome and were assessed radiographically.(VERT-NA, Harris *et al.*, 1999[72]) One RCT recorded non-vertebral fractures (not described) and vertebral fractures as adverse events, vertebral fractures were assessed by radiographs.(BMD-MN, Fogelman *et al.*, 2000[68]) Vertebral fractures were assessed by six other RCTs. (Boonen *et al.*, 2009;[60] Cohen *et al.*, 1999[65] Hooper 2005 *et al.*, 2000;[74] VERT-MN, Reginster *et al.*, 2000;[87] Reid *et al.*, 2000;[88] Ringe *et al.*, 2006 [91]) All six RCTs reported that vertebral fractures where assessed radiographically. One of these RCTs also assessed clinical vertebral and non-vertebral fractures reported as adverse events; vertebral fractures reported as adverse events included symptomatic and asymptomatic, radiographically confirmed fractures.(Boonen *et al.*, 2009[60]) One RCT assessed radiographically confirmed hip fractures and non-vertebral osteoporotic fractures; non-vertebral osteoporotic fractures, defined as all radiographically confirmed fractures of the wrist, leg, humerus, hip, pelvis, or clavicle.(McClung *et al.*, 2001[80])

Post-treatment femoral neck BMD assessment

Femoral neck BMD assessment was reported by all of the RCTs. BMD assessment was by DXA using Hologic or Lunar machines.

Zoledronate

Zoledronate was evaluated against placebo in four RCTs.(HORIZON-PFT, Black 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007;[79] Boonen *et al.*, 2012;[61] McClung *et al.*, 2009[81])

RCT location and funding

All four RCTs were international multicentre RCTs. RCT sponsor details were reported for all RCTs and were the same sponsor across RCTs. Total numbers of participants randomised ranged from 400(McClung *et al.*, 2009[81]) to 7,765.(HORIZON-PFT, Black *et al.*, 2007[58])

Populations recruited, BMD of participants and treatment dosage

Two RCTs recruited postmenopausal women with osteoporosis(HORIZON-PFT, Black *et al.*, 2007;[58] McClung *et al.*, 2009[81]) and one recruited men with osteoporosis.(Boonen *et al.*, 2012[61]) Across these RCTs, baseline BMD and T-scores would identify men and women with osteoporosis according to the current WHO definition.[2] One RCT recruited ambulatory men (24.5%) and women who had undergone repair of a hip fracture.(HORIZON-RFT, Lyles *et al.*, 2007[79]) Baseline BMD was not an inclusion criterion for this RCT. All RCTs evaluated zoledronate 5 mg intravenous infusion (i.v.) annually.

Adjuvant therapy

Adjuvant treatment in the form of calcium in combination with vitamin D was reported for all RCTs. The doses varied across the RCTs (Table 4).

Age, race, years post menopause and BMI

The mean age of participants was in HORIZON RCTs the seventh decade (between 61 and 70 years) in two RCTs,(HORIZON-PFT, Black *et al.*, 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007[79]). The mean age across participants was 66 in one trial(Boonen *et al.*, 2012[61]) and 60 in one RCT.(McClung *et al.*, 2009[81]) The mean number of years since menopause was only reported for one RCT and was 11.4 years.(McClung *et al.*, 2009[81]) Body mass index (BMI) was available for three RCTs.(HORIZON-PFT, Black *et al.*, 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007;[79] McClung *et al.*, 2009[81]) Across these RCTs, all mean BMI values were greater than 18.5 kg/m^2. Race of included participants was reported by all four RCTs across which the proportion of Caucasian participants was >90%.

Fractures at baseline

The presence of fractures at baseline was reported by three of the RCTs RCTs,(HORIZON-PFT, Black *et al.*, 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007;[79] Boonen *et al.*, 2012[61]) one of which reported all patients who were enrolled in the RCT had undergone repair of a hip fracture.(HORIZON-RFT, Lyles *et al.*, 2007[79]) One RCT reported that 28% of participants had one vertebral fracture at baseline and 35% had more than two.(HORIZON-PFT, Black *et al.*, 2007[58]) One RCT reported that 22.1% of participants had one vertebral fracture at baseline and 10.8% had more than two.(Boonen *et al.*, 2012[61])

Assessment of treatment compliance

An assessment method of compliance was not reported by any RCT evaluating zoledronate compared with placebo.

Follow-up and participants completing RCTs

Final follow-up was 24 months in two RCTs(Boonen *et al.*, 2012;[61] McClung *et al.*, 2009[81]) and 36 months in two RCTs.(HORIZON-PFT, Black *et al.*, 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007[79]) The proportion of participants completing each of the RCTs was 83.9%,(HORIZON-PFT, Black *et al.*, 2007[58]) 71.1%,(HORIZON-RFT, Lyles *et al.*, 2007[79]) 89.2%(Boonen *et al.*, 2012[61]) and 89.3%(McClung *et al.*, 2009[81]) (Table 6).

Post-treatment fracture assessment

Fractures were assessed as an outcome in three RCTs.(HORIZON-PFT, Black *et al.*, 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007;[79] Boonen *et al.*, 2012[61]) One RCT assessed vertebral fractures from radiographs.(HORIZON-PFT, Black *et al.*, 2007[58]) In this RCT clinical fracture reports were also obtained from patients at each visit. Non-vertebral fracture reports required central confirmation. Excluded were fractures of the toe, facial bone, finger and those caused by excessive trauma. In one RCT non-vertebral fractures (not a vertebral, facial, digital, or skull fracture) were confirmed when a radiograph, a radiographic report, or a medical record documented a new fracture.(HORIZON-RFT, Lyles *et al.*, 2007[79]) In this RCT a new clinical vertebral fracture was defined as new or worsening back pain with a reduction in vertebral body height. The third RCT assessed vertebral fractures from radiographs. (Boonen *et al.*, 2012[61]) In this RCT clinical fractures (vertebral and non-vertebral) were reported by participants at each visit and were verified centrally by means of a radiographic report or surgical notes.

Post-treatment femoral neck BMD assessment

Femoral neck BMD assessment by DXA was reported by all of the RCTs. Only one RCT reported the DXA model (Hologic or Lunar machines)(McClung *et al.*, 2009[81])

Head-to-head

Alendronate vs. ibandronate. One RCT evaluated alendronate compared with ibandronate in postmenopausal women.(MOTION, Miller *et al.*, 2008[83]) There was no placebo arm. This was a multicentre non-inferiority RCT conducted in The Americas, USA, Europe and South Africa. RCT sponsor details were reported. One thousand, seven hundred sixty women were randomised. Mean age was 65.6 years, mean years since menopause was 18.3, and mean BMI was 25.9 km/m^2. Race of participants was reported as 82% Caucasian. BMD inclusion criteria were based on LS (L2–L4) BMD T-score <–2.5 and ≥–5.0 SD. Previous fractures (not described) were experienced by 38.2% of the alendronate group and 39% of the ibandronate group. The alendronate dose was 70 mg per week and the ibandronate dose was 150 mg per month. Both groups also received calcium 500 mg and vitamin D 400IU per day. For compliance assessment, returned study tablets were counted. Fractures were recorded as adverse events. Follow-up was 12-months. Overall, 90% of participants completed the 12-month follow-up (Table 6).

Alendronate vs. risedronate. Five RCTs across seven publications evaluated alendronate compared with risedronate in postmenopausal women.[56,84,89,92,94,106,107] There was no placebo arm in any of these RCTs.

Three RCTs evaluated alendronate 10 mg per day and risedronate 5 mg per day.(Atmaca *et al.*, 2006;[56] Sarioglu *et al.*, 2006;[94] Muscoso *et al.*, 2004[84]) Two of these RCTs were undertaken in Turkey(Atmaca *et al.*, 2006;[56] Sarioglu *et al.*, 2006[94]) and the other in Italy.(Muscoso *et al.*, 2004[84]) Numbers of participating centres and RCT sponsor details were not reported for any of the RCTs. One RCT randomised 28 participants (14 in each group)(Atmaca *et al.*, 2006[56]) and one randomised 50 participants (25 in each group).(Sarioglu *et al.*, 2006[94]) The third randomised 2,000 participants to treatment groups also including clodronate and raloxifene. One thousand participants were randomised to risedronate and 100 (10:1 randomisation ratio) to alendronate.(Muscoso *et al.*, 2004[84]) All three RCTs reported osteoporosis to be an inclusion criterion, but only one reported a BMD T-score inclusion criterion.(Atmaca *et al.*, 2006[56]) Mean age was 66,(Atmaca *et al.*, 2006[56]) 70.5(Muscoso *et al.*, 2004[84]) and 58.8(Sarioglu *et al.*, 2006[94]) years. One RCT reported on mean years since menopause which was 15.6 years.(Atmaca *et al.*, 2006[56]) One RCT reported on mean BMI which was 27.3 km/m^2.(Sarioglu *et al.*, 2006[94]) Race was not reported by any of the three RCTs. All three RCTs prescribed adjuvant daily calcium and Vitamin D. Fractures at baseline were not reported by two of the RCTs.(Atmaca *et al.*, 2006;[56] Muscoso *et al.*, 2004[84]) In the other RCT approximately 10% of participants in both groups had vertebral fractures at baseline.(Sarioglu *et al.*, 2006[94]) Two of the RCTs reported fracture as an outcome,(Muscoso *et al.*, 2004;[84] Sarioglu *et al.*, 2006[94]) one as adverse events;(Sarioglu *et al.*, 2006[94]); however, details of the assessment method were not reported by either RCT. Final follow-up was 12 months in two RCTs(Atmaca *et al.*, 2006;[56] Sarioglu *et al.*, 2006[94]) and 24 months in the third.(Muscoso *et al.*, 2004[84]) Two of the RCTs reported 12-month femoral neck BMD assessment by DXA (Hologic – (Atmaca *et al.*, 2006)[56] Lunar – (Sarioglu *et al.*, 2006)[94]). None of the three RCTs reported on numbers withdrawing, but all reported that 100% of participants randomised were included in the analysis (Table 6).

Two further RCTs undertaken by the same study group evaluated alendronate 70 mg per week compared with risedronate 35 mg per week in postmenopausal women.(FACT, Rosen *et al.*, 2005;[92] FACTS, Reid *et al.*, 2006[89]) One was undertaken as a 12-month multicentre RCT is the USA,(FACT, Rosen *et al.*, 2006[92]) with a 12-month extension to 24 months.(Bonnick *et al.*, 2006[106]) The other undertaken as a 12-month multicentre RCT across Europe, the Americas and Asia-Pacific,(FACTS, Reid *et al.*, 2006[89]) with a 12-month extension to 24 months.(Reid *et al.*, 2008[107]) Sponsor details were the same across these RCTs. Numbers randomised were 1,053 to the USA study(FACT, Rosen *et al.*, 2006[92]) and 936 to the multinational study.(FACTS, Reid *et al.*, 2006[89]) Both RCTs recruited postmenopausal women with osteoporosis according to the current WHO definition.[2] Mean age, years since menopause and BMI was 64.5 years, 18.5 years and 25.3 km/m^2 respectively in the USA

study(FACT, Rosen *et al.*, 2005[92]) and 64.1 years, 16.9 years and 25.3 km/m^2 respectively in the international study. (FACTS, Reid *et al.*, 2006[89]) Both RCTs reported that >90% of participants were Caucasian. Both RCTs prescribed adjuvant daily calcium 1,000mg and Vitamin D 400IU.

The study undertaken in the USA reported that 12% of participants had a history of hip, spine or wrist fracture after the age of 45.(FACT, Rosen *et al.*, 2005[92]) The multinational study reported that 33.7% had a history of fractures (not described), and that 41% of participants had a family history of osteoporosis.(FACTS, Reid *et al.*, 2006[89]) Across both RCTs, clinical fractures that occurred during the trial, regardless of association with trauma or skeletal site, were reported by investigators as clinical adverse events. Femoral neck BMD was assessed in both RCTs using DXA (Hologic). Both RCTs reported a completion rate >90% at the 12-month follow-up(FACT, Rosen *et al.*, 2005;[92]FACTS, Reid *et al.*, 2006[89]) (Table 6).

Zoledronate vs. alendronate. One RCT evaluated zoledronate 5mg i.v. once annually compared with alendronate 70 mg per week.(ROSE, Hadji *et al.*, 2012[71]) There was no placebo arm. The RCT sponsor was reported. Six hundred four postmenopausal women aged 55 to 90 years with BMD T score ≤-2.0 at total hip or lumbar spine were randomised. Both groups were prescribed adjuvant calcium 1,200 mg per day and vitamin D 800IU/ per day. The mean age of participants was 67.8 years and mean BMI was 26.2 km/m^2. Thirty-three percent (33%) of participants had fractures (not described) at baseline. The proportion of participants who were current or previous smokers was 22.9%. Fractures and femoral neck BMD were not outcomes for this RCT. Quality of life was assessed using a visual analogue scale (VAS), and compliance was assessed by investigator or study personnel at each visit.(Hadji *et al.*, 2010[108]). The trialists reported that >90% participants completed the 12-month follow-up (Table 6).

Zoledronate vs. risedronate. One RCT reported as one of the HORIZON group of studies, recruited men and women aged 18 to 85 years receiving at least 7.5 mg oral prednisolone daily (or equivalent) and who were expected to receive glucocorticoids for at least another 12 months.(Reid *et al.*, 2009[90]) There was no placebo arm. The RCT which was an international multicentre RCT, categorised 416 participants receiving steroids for longer than three months as a 'treatment' subgroup and 417 participants receiving steroids for three months or less as a 'prevention' subgroup; both subgroups were randomised to zoledronate 5 mg i.v. once annually or risedronate 5 mg per day. The sponsor was reported. All treatment groups were prescribed adjuvant calcium 1,200 mg per day and vitamin D 800IU per day. Across treatment groups 31% were male. Mean age of all participants was 54.41 years. Race was

not reported. Follow-up was at 12 months. Vertebral fractures were assessed by radiograph and femoral neck BMD by DXA (Hologic or Lunar). EQ-5D health-related quality-of-life was assessed.[111] The trialists reported that >90% participants completed the 12-month follow-up (Table 6).

5.2.1.2 Quality of the available research

Twenty-one of the 46 included RCTs were considered to be at low risk of selection bias[47,49,57-59,61,66,69-72,74,75,79,81,83,89,90,92,95,96]. However, the majority (25/46) of included RCTs did not report a method of random sequence generation and were therefore classified as being at unclear risk of selection bias. A summary of all risk of bias criteria judgements by RCT is reported in Figure 4. A summary about each risk of bias item presented as percentages across all included RCTs is presented in Figure 5.

Twelve of the 46 included RCTs[57,58,61,66,70,72,79,81,83,89,90,92] reported appropriate methods for concealment of treatment allocation and were therefore judged to be at low risk of bias for this domain. The remaining RCTs did not report on allocation concealment and were therefore judged as being at unclear risk of bias for this domain.

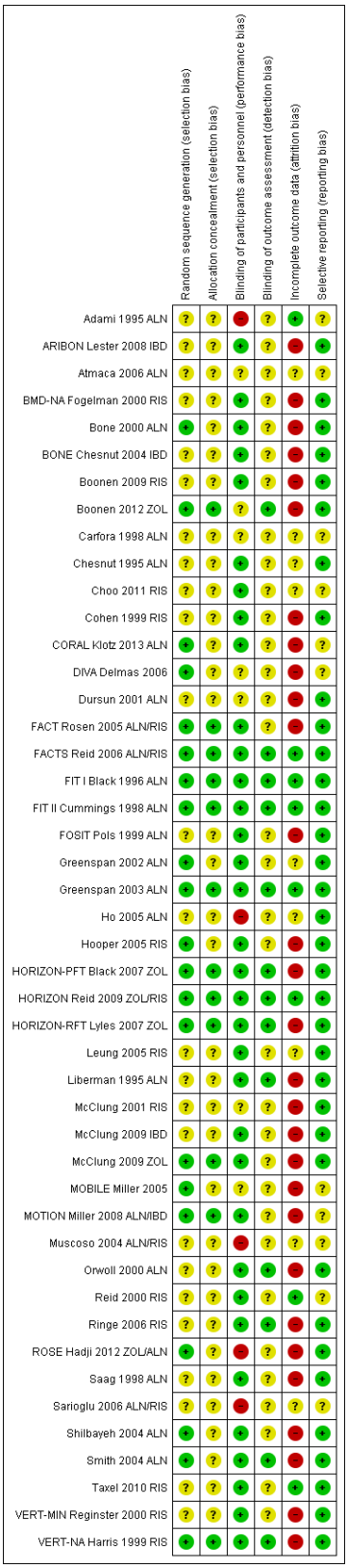
Thirty-four of the included RCTs[45,57-60,63-66,68-70,72,74-79,81,82,85-93,95-97] reported that participants and personnel were blind to treatment allocation and were therefore judged at low risk of performance bias. Five RCTs were reported as either open label or single blind and were judge at high risk of bias.(Adami *et al.*, 1995;[55] Ho *et al.*, 2005;[73] Muscoso *et al.*, 2004;[84] ROSE, Hadji *et al.*, 2012;[108] Sarioglu *et al.*, 2004[94]). The remaining RCTs did not report on blinding and were considered at unclear risk of bias for this domain.

Blinding of the outcome assessment was reported by thirteen RCTs,[57,58,61,66,70,72,78,79,85,89-91,96] which were therefore classified as being of low risk of detection bias. The remaining RCTs were considered at unclear risk of bias for this domain.

In twenty-nine of the 46 RCTs,[47,49,58,60,61,65,68,71,72,75,78,80-83,85-87,91,93,95,96,112-118] attrition was reported to be ≥10% across treatment groups. These RCTs were judged to be at high risk of attrition bias. In eight of the included RCTs attrition across treatment groups was reported as less than 10%.(Adami *et al.*, 1995;[55] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings et al, 1998;[66] Greenspan *et al.*, 2003;[70] Taxel *et al.*, 2010[97], Reid *et al.*, 2000;[88] Reid *et al.*, 2006;[89] Reid *et al.*, 2009;[90]). These RCTs were judged at low risk of attrition bias. In the remaining eight RCTs, numbers withdrawing were not reported, these RCTs were therefore considered as unclear risk of bias for this domain.

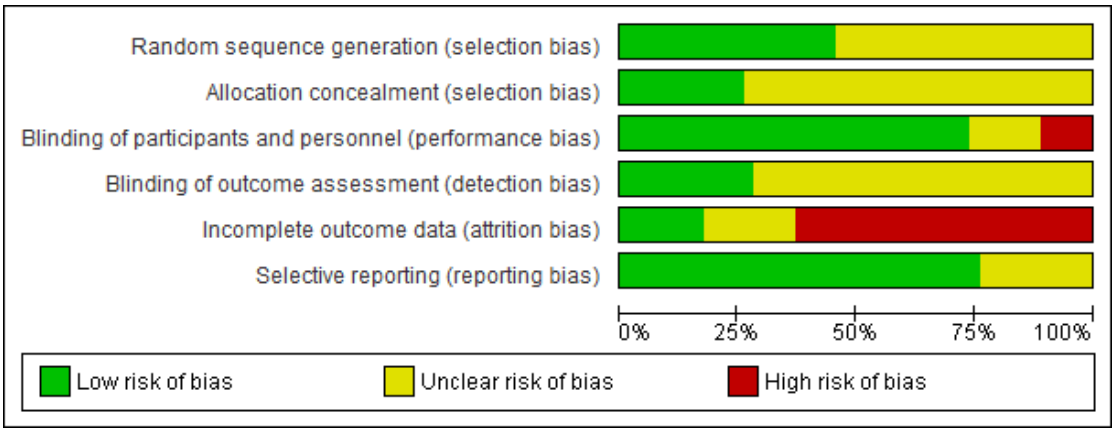
Thirty-four of the included RCT reports[45,57-61,65-74,76-82,85-87,89-93,95-97] contained either reference to a RCT protocol or a RCT registration number, and were therefore judged as being at low risk of selection bias. The remaining included RCTs did not contain this information and were therefore judged at unclear risk of bias for this domain.

Figure 4: Risk of bias summary: judgements about each risk of bias item for each included RCT



?, unclear risk of bias; +, low risk of bias, -, high risk of bias

Figure 5: Risk of bias graph: judgements about each risk of bias item presented as percentages across all included RCTs



5.2.2 Assessment of effectiveness

Outcome measures pre-specified in the final protocol (see Appendix 1) reported across the included RCTs are presented in Table 6.

a) Fracture

A total of 27 RCTs provided suitable fracture data for inclusion in the network meta-analysis reported in section 5.2.2.2 of this assessment report. Nine evaluating alendronate compared with placebo,(Bone *et al.*, 2000;[59] Carfora *et al.*, 1998;[63] Dursun *et al.*, 2001;[67] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings 1998;[66] FOSIT, Pols *et al.*, 1999;[86] Greenspan *et al.*, 2002;[69] Liberman *et al.*, 1995;[78] Orwoll *et al.*, 2000[85]) three evaluating ibandronate against placebo,(ARIBON, Lester *et al.*, 2008;[76] BONE, Chesnut *et al.*, 2004;[45] McClung *et al.*, 2009[82]) nine evaluating risedronate against placebo, (Boonen *et al.*, 2009;[60] Cohen *et al.*, 1999;[65] BMD-MN Fogelman *et al.*, 2000;[68] Hooper *et al.*, 2005;[74] McClung *et al.*, 2001;[80] Reid *et al.*, 2000;[88] Ringe *et al.*, 2006;[91] VERT-USA Harris *et al.*, 1999;[72] VERT-EU Reginster *et al.*, 2000[87]), three evaluating zoledronate compared with placebo,(Boonen *et al.*, 2012;[61] HORIZON-PFT Black 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007[79]) one evaluating alendronate compared with ibandronate,(MOTION, Miller *et al.*, 2008[83]) one evaluating alendronate compared with risedronate,(Muscoso *et al.*, 2004[84]) and one evaluating zoledronate compared with risedronate.(HORIZON, Reid *et al.*, 2009[90])

Alendronate

In the FIT I trial, Black *et al.* (1996) [57] reported a relative risk of 0.53 (95%CI 0.41 to 0.68) for morphometric vertebral fractures, a relative hazard of 0.45 (95%CI 0.27 to 0.72) for clinical vertebral fractures and 0.72 (95%CI 0.58 to 0.90) for the risk of any clinical fracture at the 36-month follow-up. The relative hazards for hip fracture and wrist fracture were

reported as 0.49 (95%CI 0.23 to 0.99) and 0.52 (95%CI 0.31 to 0.87) respectively. In the FIT II trial, Cummings *et al.* (1998)[66] reported a relative risk for radiographic vertebral fractures at 36 months of 0.65 (95%CI 0.39 to 0.80). The relative hazard of clinical fractures (vertebral, hip or wrist) was reported as 0.64 (95%CI 0.50 to 0.82) in women with osteoporosis and 1.08 (95%CI 0.87 to 1.35) in those without osteoporosis. In the RCT by Carfora *et al.* (1998)[62] vertebral fractures were reported for 8.82% of placebo compared with 2.94% of alendronate participants. The RCT by Dursun *et al.* (2001)[67] reported vertebral fracture at 12 months of 40.0% in the group assigned to calcium and 31.6% in the alendronate combined with calcium group. The difference between treatments in these RCTs was not reported. In men, Orwoll *et al.*, 2000[85] reported a significant difference between treatments at 24 months in new vertebral fractures (p=0.02) but not non-vertebral fractures (p=0.8).

Across the RCTs assessing fractures as adverse events, Bone *et al.* (2000)[59] reported that the difference between treatments in non-vertebral fractures (foot, ankle, rib) was not significant (p-value not reported). Greenspan *et al.*, (2002)[69] and Greenspan *et al.*, (2003)[70] both reported that the difference between treatments in clinical fractures (not described) was not significant (p-values not reported). In the FOSIT trial, Pols *et al.* (1999)[86] reported a 47% risk reduction in non-vertebral fractures (95%CI 10 to 70; p=0.021). In the CORAL trial, Klotz *et al.* (2013) reported no statistically significant difference between treatments in fractures (not described), p-value 0.4395.

Across the two RCTs that pooled fracture data across alendronate dosing arms (licensed and unlicensed doses), Liberman *et al.* (1995) reported a difference between treatments in vertebral fractures at 36 months for alendronate 5 mg, 10 mg and 20 mg groups combined compared with placebo of RR 0.52 (95%CI 0.28 to 0.95); p=0.03; and non-vertebral fractures of RR 0.79 (95%CI 0.52 to 1.22) (p-value not reported). A difference between treatments for placebo compared with alendronate 10mg per day was reported for this RCT as an odd ratio (0.45, 95%CI 0.18 to 1.13; p-value not reported).[99] However, numbers by group were not reported. Saag *et al.* (1998)[93] reported a difference between treatments in vertebral fractures at 12 months for alendronate 5 mg and 10 mg groups combined compared with placebo RR 0.6 (95%CI 0.1 to 4.4).

Ibandronate

In the ARIBON trial, Lester 2008 *et al.* (2008)[76] reported that three patients in placebo and two patients in the ibandronate group experienced fractures as adverse events. McClung *et al.*, (2009)[82] also reported fractures as adverse events with 2% in placebo and 3% in the ibandronate group experiencing fractures. A difference between treatments was not reported

by either RCT. In the BONE trial, Chesnut *et al.*, (2004)[45] reported a difference between treatments in risk reduction for ibandronate 2.5 mg per day compared with placebo for new vertebral fractures at 36 months of 62% (95%CI 41 to 74), p=0.0001. Clinical non-vertebral fractures were experienced by 8.2% of placebo compared with 9.1% of the 2.5mg per day group. A difference between treatments was not reported. In the DIVA study, Delmas *et al.* (2006)[49] reported that 43 (3.1%) of all participants experienced clinical fractures including non-vertebral fractures recorded as adverse events at 12 months, 17 in the 2.5 mg per day group and 13 in the 3 mg i.v. every three months group. The corresponding numbers at the 24-month follow-up were 29 (6.2%) and 23 (4.9%).[50] Differences between treatments were not reported. In the MOBILE study, Miller *et al.*, (2005)[47] reported that there was no statistically significant difference between treatments in clinical fractures recorded as adverse events at 12 months. At the 24-month follow up 24 (6.1%) of participants receiving ibandronate 2.5 mg per day and 27 (6.8%) receiving 150 mg per month had clinical fractures.[48] Differences between treatments were not reported.

Risedronate

In men, Boonen *et al.* (2009)[60] reported no differences in new vertebral or clinical fractures (recorded as adverse events) between risedronate 35 mg per week of placebo at 24 months. Across both men and women, Cohen *et al.*, (1999) reported no statistically significant difference between risedronate 5 mg per day or placebo on vertebral fractures at 12 months (p=0.072). In the RCT assessing fracture as adverse events (BMD-MN, Fogelman *et al.*, 2000[68]) 14% of the placebo group experienced vertebral fractures and 9% experienced non-vertebral fractures at 24 months. Corresponding numbers in the risedronate 5 mg group were 7% and 5% respectively. A difference between treatments was not reported. The difference between treatments in new vertebral fractures or non-vertebral fractures between risedronate 5 mg per day and placebo at 24 months was reported as not significant (p-value not reported) by one RCT (Hooper *et al.*, 2005[74]). In the BMD-MN trial, Fogelman *et al.* (2000)[68] assessed fractures as adverse events. At the end of the study, vertebral fractures were present in 14% in the placebo group, and 7% in the 5- mg risedronate group. Non-vertebral fractures occurred 9% in the placebo group, compared with 5% in the group. A difference between treatments was not reported.

In the VERT-NA trial, Harris *et al.* (1999)[72] reported a difference between treatments in the incidence of vertebral fractures at 36 months of 41% (95%CI 0.18-0.58; p=0.003) and non-vertebral fractures of 39% 95%CI 6 to 61%; p=0.02). In the 60-month extension, fractures were recorded as adverse events, the trialists reporting that adverse events were similar across groups.(VERT-NA, Ste-Marie *et al.*, 2004[101]) A difference between treatments for fractures

was not reported. In the VERT-MN trial, Reginster *et al.* (2000)[87] reported a difference between treatments in new vertebral fractures of RR 0.51 (95%CI 0.36-0.73; p<0.001) and non-vertebral fractures of RR 0.67 (95%CI 0.44-1.04; p=0.063) at the 36-month follow-up. In the extension study (VERT-MN, Sorensen *et al.*, 2003 [102]) a difference between treatments in vertebral fractures of 59% (95%CI 0.19-0.79; p=0.01) was reported. The trialists reported that fracture results observed in the study extension were consistent with those observed in the first three years.

In the subgroup of women aged 70 to 79, McClung *et al.* (2001)[80] reported a difference between treatments in hip fracture between risedronate 5 mg per day compared with placebo at 12 months of RR 0.7 (95%CI 0.4 to 1.1). In the subgroup of women aged 80 plus, hip fracture data were reported for the difference between treatments of the 2.5 mg per day group (unlicensed) and the 5 mg per day group combined compared with placebo (p=0.35). The hip fracture results across all women were also reported for a comparison between the 2.5 mg per day group and 5 mg per day group data combined compared with placebo (p=0.02).

Reid *et al.* (2000)[88] reported a p-value for the difference between treatments in vertebral fractures at 12 months across men and women for the risedronate 2.5 mg per day group and 5 mg per day group combined compared with placebo of 0.042. The difference between treatments for 5 mg per day compared with placebo was not reported. The trialists reported that the RCT was not powered to demonstrate fracture efficacy.

Ringe *et al.* (2006)[91] reported a difference between treatments at 12 months in new vertebral fractures in men of p=0.028. The difference between treatments at 24 months was reported as p=0.032 (Ring *et al.*, 2009[103]).

Zoledronate

In the HORIZON-PFT trial, Black *et al.* (2007)[60] reported a difference between treatments in morphometrically assessed vertebral fractures in women at 36 months between zoledronate 5 mg annually and placebo of RR 0.30 (95%CI 0.24 to 0.38; p<0.001) in women not taking any osteoporosis medications at baseline (Stratum I). Significant between group differences across all women were also reported for hip fracture, non-vertebral fractures, clinical fractures and clinical vertebral fractures (p<0.001).

In the HORIZON-RFT trial, Lyles *et al.* (2007) [79] reported a difference between treatments in any new clinical fracture at 36 months for zoledronate 5 mg annually compared with placebo n men and women as a hazard ratio (HR) 0.65 (95%CI 0.50 to 0.84; p=0.001). The difference

between treatments in clinical non-vertebral fractures was reported as HR 0.73 (95%CI 0.55 to 0.98); p=0.03), clinical hip as HR 0.70 (95%CI 0.41 to 1.19; p=0.18), and clinical wrist as HR 0.72 (95%CI 0.56 to 0.93; p=0.01).

In men, Boonen *et al.* (2012)[61] reported a difference between treatments in participants experiencing one or more new morphometric vertebral fracture at 24 months as RR 0.33 (95%CI 0.16-07.70; p=0.002).

Alendronate *vs.* risedronate

In the MOTION trial, Miller *et al*., (2008)[83] reported that at 12 months 18/874 (2.1%) of participants in the ibandronate group had experienced osteoporotic fractures recorded as adverse events of which five were vertebral fractures and 14 non-vertebral, compared with 17/859 (2%) overall five vertebral and 12 non-vertebral in the alendronate group. A difference between treatments was not reported.

Alendronate *vs.* risedronate

Muscoso *et al*., (2004)[84] reported that at 24 months there were four fractures in the risedronate group compared with none in the alendronate group. However, it was unclear if the unit of analysis was the participant or the fracture. A difference between treatments was not reported. In the FACT trial, Rosen *et al.* (2005)[92] reported that at 12 months 5.0% of the alendronate group had an adverse event fracture compared with 3.8% in the risedronate group. A difference between treatments was not reported. The respective values at 24 months (FACT, Bonnick *et al.*, 2005[106]) were 8.3% and 8.2%. In the FACTS trial, Reid *et al.* (2006)[89] reported that at 12 months 3.6% of the alendronate group had an adverse event fracture compared with 3.8% in the risedronate group. A difference between treatments was not reported. The respective values at 24 months (FACTS, Reid *et al.*, 2008[107]) were 5.7% and 6.3%.

Zoledronate *vs.* risedronate

In the HORIZON trial, Reid *et al.* (2009)[90] reported that the frequency of new vertebral fractures was zoledronic acid (n=5) and risedronate (n=3), with no significant difference between drug groups. Data by steroid use subgroup were not reported.

b) Femoral neck BMD

A total of 35 RCTs provided suitable femoral neck BMD data for inclusion in the network meta-analysis reported in section 5.2.2.2 of this assessment report. Twelve evaluating alendronate compared with placebo,(Adami *et al.*, 1995;[55] Bone *et al.*, 2000;[59] CORAL, Klotz

et al., 2013;[75] Dursun *et al.*, 2001;[67] FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] FOSIT, Pols *et al.*, 1999;[86] Greenspan *et al.*, 2002;[69] Greenspan *et al.*, 2003;[70] Liberman *et al.*, 1995;[78] Orwoll *et al.*, 2000;[85] Saag *et al.*, 1998[93]) two evaluating ibandronate compared with placebo,(BONE, Chesnut *et al.*, 2004;[45] McClung *et al.*,2009[82]) one evaluating ibandronate 2.5 mg per day compared with 3 mg i.v. every three months,(DIVA, Delmas *et al.*, 2006[49]) one evaluating ibandronate 2.5 mg per day compared with 150 mg per month,(MOBILE, Miller at el., 2005[47]) ten evaluating risedronate compared with placebo,(BMD-MN, Fogelman *et al.*, 2000;[68] Boonen *et al.*, 2009;[60] Choo *et al.*, 2011;[64] Cohen *et al.*, 1999;[65] Hooper *et al.*, 2005;[74] Leung *et al.*, 2005;[77] Reid *et al.*, 2000;[88] Taxel *et al.*, 2010;[97] VERT MN, Reginster *et al.*, 2000;[87] VERT NA Harris *et al.*, 1999[72]) four evaluating zoledronate compared with placebo,(Boonen *et al.*, 2012; HORIZON-PFT, Black *et al.*, 2007;[58] HORIZON-RFT, Lyles *et al.*, 2007;[79] McClung et al, 2009[81]) two evaluating alendronate compared with risedronate,(FACT, Rosen *et al.*, 2005;[92] FACTs, Reid *et al.*, 2006[89]) one evaluating alendronate compared with ibandronate,(MOTION, Miller *et al.*, 2008[83]) one evaluating risedronate compared with alendronate,(Sarioglu *et al.*, 2006[94]) and one evaluating zoledronate compared with risedronate.(HORIZON, Reid *et al.*, 2009[90])

Alendronate

Statistically significant differences between treatments for alendronate 10 mg per day were reported at 48 weeks by one trial,(Saag *et al.*, 1998[93]) at 12 months by three RCTs,(Dursun *et al.*, 2001;[67] Ho *et al.*, 2005;[73] Pols *et al.*, 1999[86]) at 24 months by four RCTs,(Adami *et al.*, 1995;[55] Bone *et al.*,2000;[59] Chesnut *et al.*,1995;[63] Orwoll *et al.*, 2000 [85]) and at 36 months by three RCTs.(FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Liberman *et al.*, 1995[78]) The variance estimates were reported as a standard error in FIT I (Black *et al.*, 1996[57]), however FIT II, reported that the variance estimates were standard deviations (Cummings *et al.*, 1998[66]). These trialists were contacted for confirmation of the variance estimate (email communication 16 March 2015). No reply was received to 27 March 2015. For this assessment report it was assumed that the femoral neck BMD variance estimate was a standard error for both RCTs due to the sample sizes and apparent comparability of the reported values. A mean difference between treatments at 24 months of 3.4% (95%CI, 2.3% to 4.4%) was reported by one RCT (Greenspan *et al.*, 2002[69]) (p-value not reported). One RCT did not report the difference between treatments at 36-months (data by group presented in graphical format only) (Greenspan *et al.*, 2003[70]). One RCT reported mean percent change from baseline compared with age-matched and young adult reference values (source not reported)(Shilbayeh *et al.*,[95]) Significant changes from baseline in the alendronate group were reported ($p<0.01$). One RCT reported differences between treatments in femoral neck T-scores and Z-scores at 12 months (Smith *et al.*, 2004 [96]). No statistically significant

differences between treatments were reported. One RCT assessing alendronate 70 mg per week reported a mean change from baseline in femoral neck BMD 12 months of -2.06% (±5.71) in the placebo group compared with 1.65% (±7.53) in the alendronate group.(Klotz *et al.*,2013[75]) A difference between treatments was not reported by this RCT.

Ibandronate

One RCT assessing ibandronate 150 mg per month reported a mean change from baseline in femoral neck BMD 12 months of -0.73% (±4.16 SD) in the placebo group compared with 1.09% (±2.87 SD) in the ibandronate group.(McClung *et al.*, 2009[82]) A difference between treatments was not reported by this RCT. In the DIVA trial, Delmas *et al.* (2006)[49] reported a mean change from baseline at 12 months of 1.6% (±4.18 SD) with ibandronate 2.5 mg per day compared with 2.3 (±3.87 SD) with ibandronate 3 mg i.v. every three months. Corresponding values at 24 months were 2.01 (±5.65 SD) and 2.32 (±4.70 SD) repectively.[50] Differences between treatments were not reported. In the MOBILE trial, Miller *et al.* (2005)[47] reported a mean change from baseline at 12 months of 1.71% (±3.68 SD) with ibandronate 2.5 mg per day compared with 2.22 (±3.83 SD) with ibandronate 150 mg per month. Corresponding values at 24 months were 1.91 (±4.45 SD) and 3.12 (±7.03 SD) repectively.[48] Differences between treatments were not reported.

Risedronate

Statistically significant differences between treatments were reported in women receiving 5 mg per week compared with placebo at 12 months,(Leung *et al.*, 2005[77]) 24 months(BMD-MN, Fogelman *et al.*, 2000;[68] Hooper *et al.*, 2005;[74]), 36 months(VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000[87]) and at 60 months(VERT-MN, Sorensen *et al.*, 2003 [102]) Statistically significant differences between treatments were reported for men receiving 35 mg per week at 6 months (Taxel *et al.*, 2010[97]) and at 24 months,(Boonen *et al.*, 2009[60]) and men receiving 5 mg per week at 12 months(Ringe *et al.*, 2006[91]) and 24 months(Ringe *et al.*, 2009[103]). One RCT reported a p-value for risedronate 35 mg per week of 0.4670, but it was unclear whether this was compared with baseline or the placebo group.(Choo *et al.*, 2011[64]). One RCT reported a statistically significant difference between treatments between risedronate 5 mg per day and placebo at 12 months across men and women ($p<0.001$), however the difference between treatments across women only was not significant.(Cohen *et al.*, 1999 [65]) McClung *et al.* (2001) reported a difference between treatments of 3.4% for risedronate 5 mg per week compared with placebo in the subgroup of women aged 70 to 79.(McClung *et al.*, 2001[80]) Data by group or a p-value were not reported. Reid *et al.* (2000)[88] reported $p<0.05$ for risedronate 5 mg in postmenopausal women compared with baseline.

Zoledronate

In the HORIZON-PFT trial, Black *et al.* (2007)[60] reported a difference between treatments at 36 months of 5.06% (95%CI 4.76-5.36; p<0.001). In the HORIZON-RFT trial, Lyles *et al.* (2007)[79] also reported a statistically significant between-group at 36 months (p<0.001). In men, Boonen *et al.* (2012)[61] reported a statistically significant between-group at 24 months (p<0.05). In postmenopausal women McClung *et al.* (2009)[81] also reported a statistically significant between-group at 24 months (p<0.001).

Alendronate *vs.* ibandronate

In the MOTION trial, Miller *et al.*, 2008[83] reported a mean change from baseline in femoral neck BMD 12 months of 2.1% (±1.77 SD) in the alendronate 70 mg per week group compared with 2.3% (±2.12 SD) in the ibandronate 150 mg per months group. The difference between treatments was not reported.

Alendronate *vs.* risedronate

In the RCT by Sarioglu *et al.* (2006)[94] data and variance estimates by group were reported. The trialists reported that the difference between treatments was not significant (p-value or difference between treatments not reported). In the FACT trial, Rosen *et al.* (2005)[92] reported that at 12 months the difference between treatments was 0.7% (95%CI 0.1 to 1.2; p<0.005) in favour of alendronate. The difference between treatments at 24 months (FACT, Bonnick *et al.*, 2005[106]) was reported as 0.8% (95%CI 0.3 to 1.4%; p<0.005) in favour of alendronate. In the FACTS trial, Reid *et al.* (2006)[89] reported that at 12 months the difference between treatments was 0.56% (95%CI 0.03 to 1.09; p=0.039) in favour of alendronate. The difference between treatments at 24 months (FACTS, Reid *et al.*, 2008[107]) was reported as 1.0% (95% CI: 0.3 to 1.6%; p=0.002) in favour of alendronate.

Zoledronate *vs.* risedronate

In the HORIZON trial, Reid *et al.* (2009)[90] reported that in the treatment subgroup the difference between treatments at 12 months was 1.06% (95%CI 0.32 to 1.79). The difference between treatments in the prevention subgroup was 1.33% (95%CI 0.41 to 2.25). Both were in favour of zoledronate.

c) Mortality

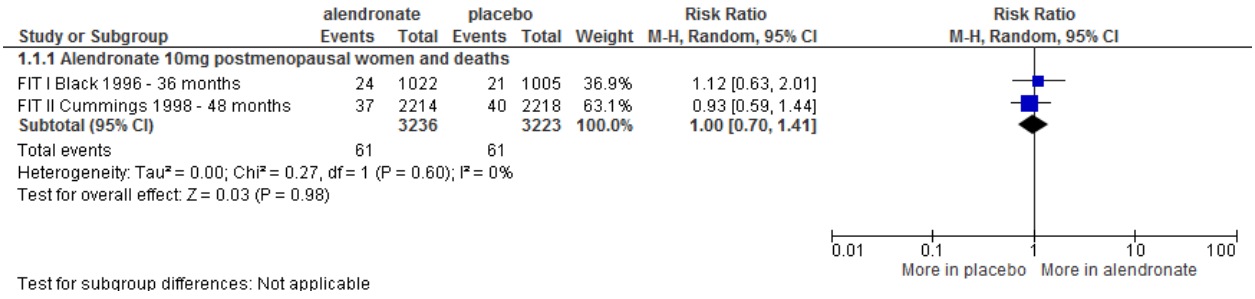
Details of all adverse events reported for alendronate, ibandronate, risedronate, and zoledronate, across all included RCTs are presented in Appendix 5.

Nine RCTs[45,57,58,60,61,66,79,83,90] reported deaths in participants treated with bisphosphonates; of which two [57,66] evaluated deaths in alendronate 10mg/day compared with placebo, one[45] ibandronate 2.5mg/day compared with placebo, one[60] risedronate compared with placebo, four[58,61,79,90] zoledronate 5mg/year compared with placebo, and one[83] was a head-to-head comparison between alendronate and ibandronate. The frequencies of deaths in each treatment group in the included RCTs are tabulated in Appendix 5.

Alendronate

Two RCTs; FIT I-Black *et al.*, 1996[57] and FIT II-Cummings *et al.*, 1998[66] reporting adverse events in postmenopausal women for 24 months and 48 months respectively were included. Data from the two RCTs show that there were 122 deaths; 1.9% (61/3236) in alendronate compared with 1.9% (61/3223) in placebo; (pooled risk ratio (RR): 1.0, 95% CI: 0.70 to 1.41, p = 0.98). The difference between treatments was not statistically significant (Figure 6).

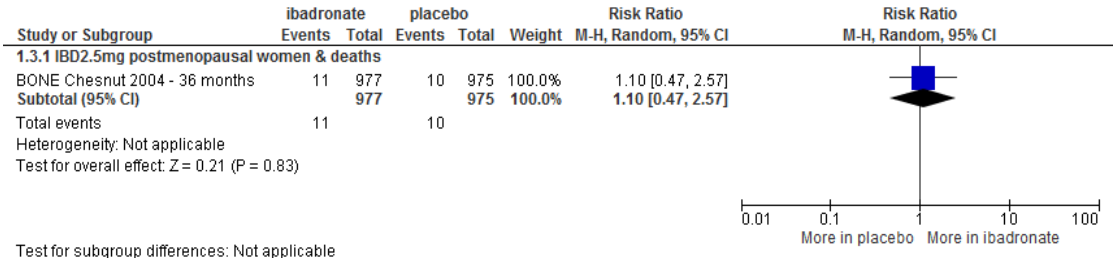
Figure 6: Forest plot - Deaths in postmenopausal women on alendronate compared with placebo



Ibandronate

The BONE trial-Chesnut *et al.* (2004)[45] investigated ibandronate 2.5mg/daily compared with placebo for 36 months in postmenopausal women. They also did not find any association between any treatment group and risk of death. In total 22 deaths occurred; 1.1% (11/977) in ibandronate 2.5mg compared with 1.0% (10/975) in placebo (RR: 1.10, 95% CI: 0.47 to 2.57, p = 0.83). The difference between treatments was not statistically significant Figure 7.

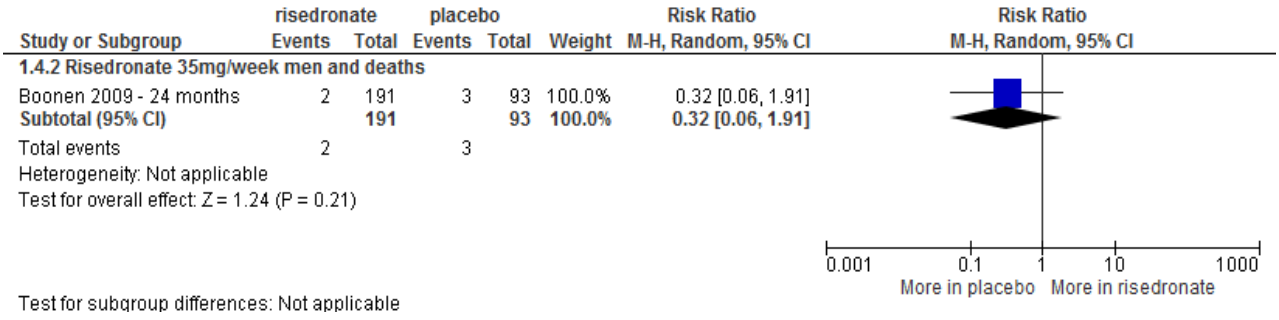
Figure 7: Forest plot - Deaths in postmenopausal women and men on ibandronate compared with placebo



Risedronate

Boonen *et al.* (2009)[60] evaluated risedronate 35mg/week in osteoporotic men. At 24 months of follow-up, there were 5 deaths; 1% (2/191) in participants on risedronate died compared with 3% (3/93) in placebo (RR: 0.32, 95% CI: 0.06 to 1.91, p = 0.21). The difference between treatments was not statistically significant (Figure 8).

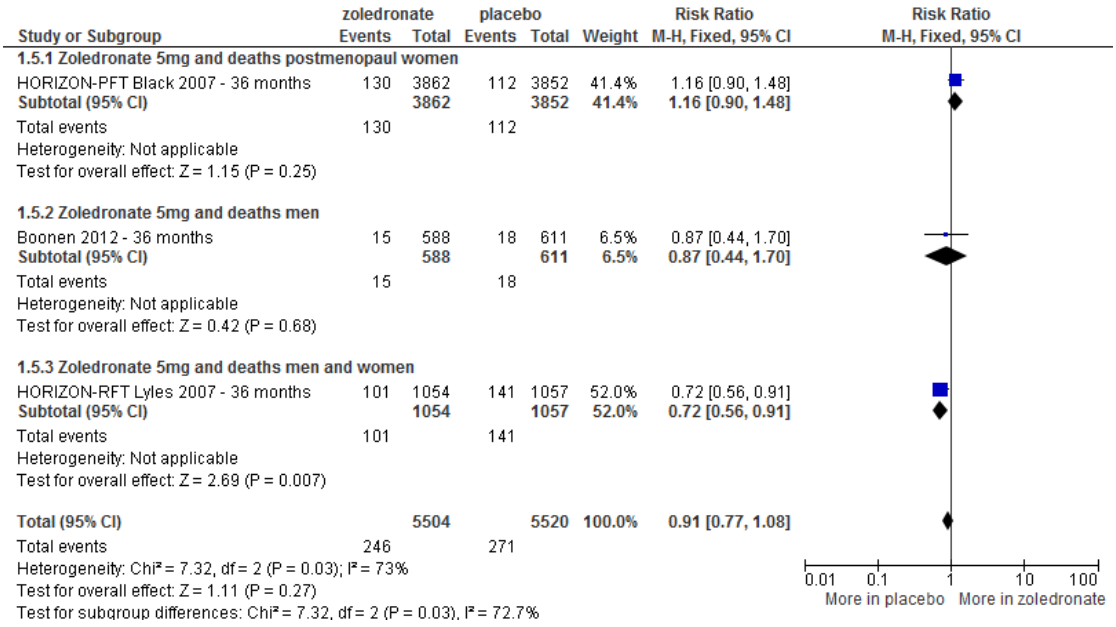
Figure 8: Forest plot - Deaths osteoporotic women & men on risedronate compared with placebo



Zoledronate

Three RCTs: HORIZON-PFT, Black et al, (2007)[58] evaluating zoledronate 5mg compared with placebo in postmenopausal women at 36 months, Boonen *et al.* (2012)[61] evaluating zoledronate 5mg compared with placebo in men for 36 months, and HORIZON-RFT, Lyles *et al.* (2007)[79] evaluating zoledronate 5mg compared with placebo in men and women following hip fracture at 36 months reported mortality. The pooled number of deaths across these RCTs was 517; of which 4.5% (246/5504) were across the zoledronate 5mg groups and 4.9% (271/5520) in the placebo groups (pooled RR: 0.91, 95% CI: 0.77 to 1.08, p = 0.28). The difference between treatments was not statistically significant. However, the difference between treatments for the HORIZON-RFT[79] RCT alone was statistically significant (p=0.007) with a greater percentage of deaths in the placebo arm (Figure 9).

Figure 9: Forest plot - Deaths men or women on zoledronate 5mg/year compared with placebo



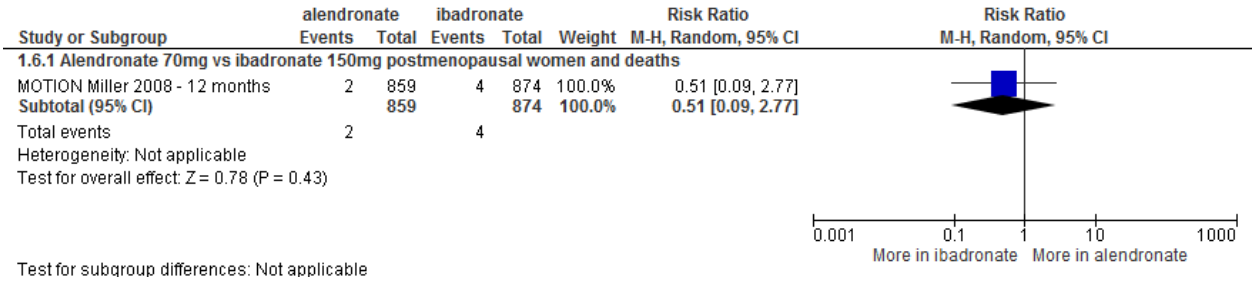
Head-to-Head - Zoledronate compared with risedronate

HORIZON, Reid *et al.*, 2009[90] compared zoledronate 5mg with risedronate 5mg per day in both men and women receiving steroids divided into treatment and prevention subgroups for 12 months. The difference between treatments in mortality in the treatment subgroup was RR 0.33 (95%CI 0.04 to 3.20, p=0.34) and the difference between treatments in the prevention subgroup was RR 3.06 (95%CI 0.13 to 74.57, p=0.49). The differences between treatments were not statistically significant. Forest plot not presented.

Head-to-Head - Alendronate compared with ibandronate

One head-to-head RCT evaluating alendronate 70mg/per week compared with ibandronate 150mg/per month in postmenopausal women reported mortality at 12 months (MOTION, Miller *et al.*, 2008[83]). In total 6 deaths were reported in active treatment and placebo; 0.2% (2/859) compared with 0.5% (4/874) respectively (RR: 0.51, 95% CI: 0.09 to 2.77, p = 0.43) (Figure 10).

Figure 10: Forest plot - Head-to-head alendronate 70mg compared with ibandronate 150mg in postmenopausal women and deaths



d) Adverse effects of treatment

Details of all adverse events reported for alendronate, ibandronate, risedronate, and zoledronate, across all included RCTs are presented in Appendix 5.

Twenty-six of the included RCTs reported adverse events.[45,57-61,65,66,68,69,71,72,74,78-83,85-87,90,92,104,119] Twenty of these reported on any adverse event,[45,57-61,68,69,71,72,74,79-83,86,87,89,90,92] and nineteen reported on any serious adverse event.[45,58-61,68,71,72,74,79,80,82,83,85-87,89,90,92] Twenty RCTs reported the number of participants withdrawing due to adverse events.[45,57-60,66,68,71,72,74,78-80,82,85-87,89,90,92] Twenty RCTs reported data on upper gastrointestinal (GI) events.[45,57-60,66,68,71,72,74,78-80,82,85-87,90,92,119] Six of these evaluated alendronate compared with placebo,[57,59,66,69,85,86] six evaluated risedronate compared with placebo,[60,68,72,74,80,87] one evaluated ibandronate compared with placebo,[82] one evaluated zoledronate compared placebo,[104] two evaluated alendronate compared with risedronate,[92,119] and one evaluated alendronate compared with zoledronate.[71] Ten RCTs reported influenza-like symptoms.[58,60,61,71,79,81-83,85,90.] Five of these RCTs evaluated zoledronate.[58,61,79,81,90] one evaluated alendronate,[85] one evaluated ibandronate,[82] and one evaluated risedronate[60]. Two RCTs reporting influenza-like symptoms were head-to-head comparisons of alendronate 70 mg/week compared with ibandronate 150mg/month[83] and alendronate 70mg/week compared with zoledronate 5mg/year[71].

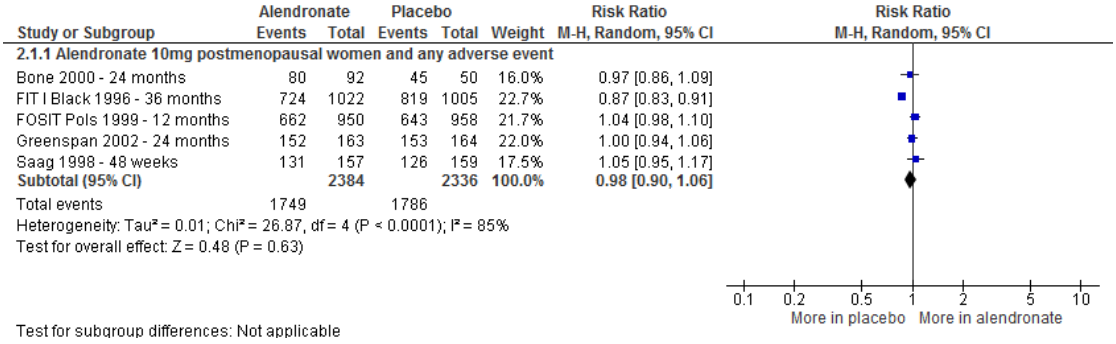
Any adverse events/ serious AEs/ and withdrawals due to adverse events

Alendronate

Five RCTs reported any adverse event associated with alendronate 10mg and placebo in postmenopausal women for treatment periods ranging from 12 to 36 months.(Bone *et al.*, 2000;[59] FIT I, Black *et al.*, 1996;[57] FOSIT, Pols *et al.*, 1999;[86] Greenspan *et al.*, 2002;[69] Saag *et al.*, 1998[93]) Across these RCTs there were 3535 adverse events; of which 73.3% (1749/2384) occurred in participants on alendronate compared with 76.4% (1786/2336)

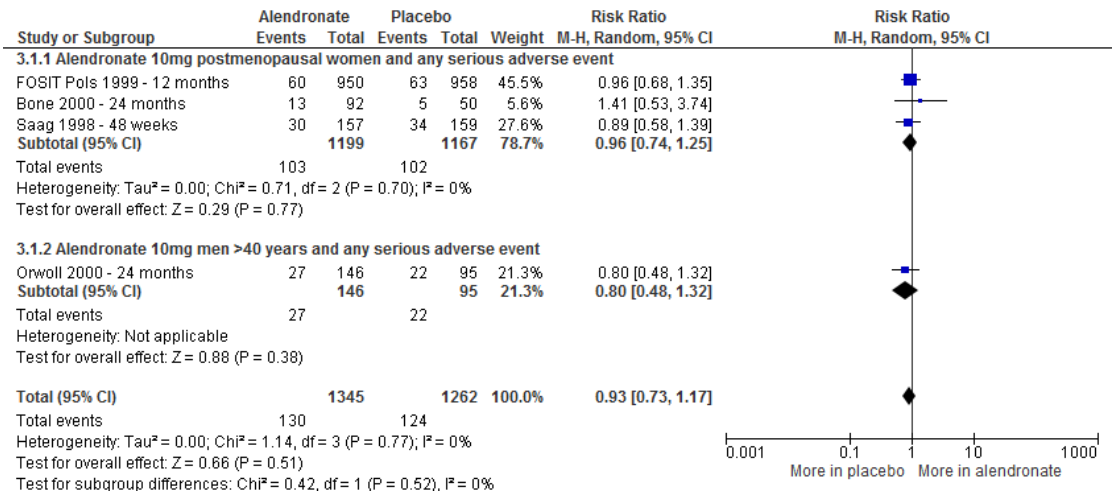
among those on placebo (pooled RR: 0.98, 95% CI 0.90 to 1.06, p = 0.63). The difference between treatments was not statistically significant (Figure 11)

Figure 11: Forest plot - Any adverse event in alendronate compared with placebo



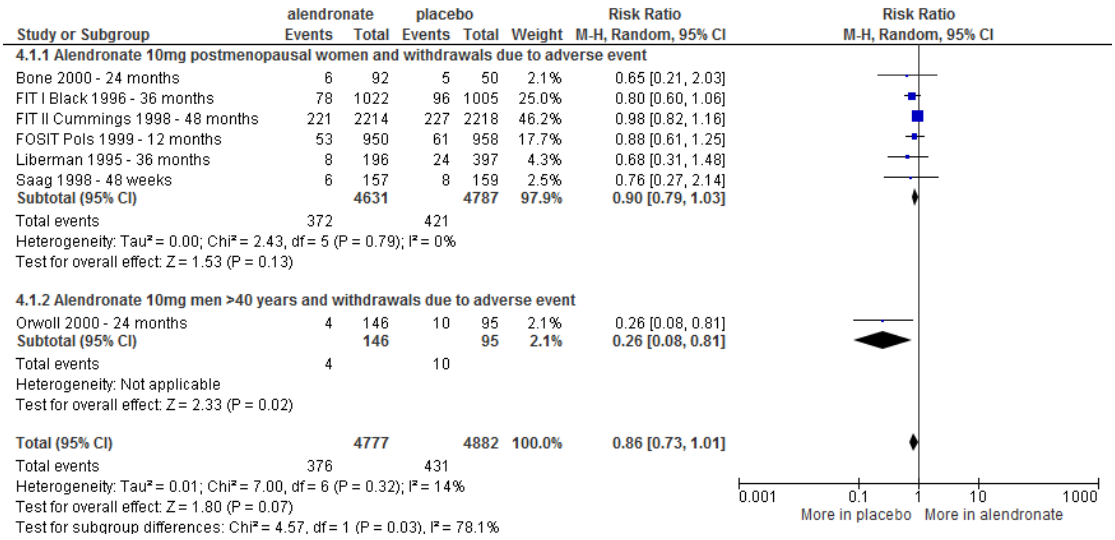
Three RCTs reported the proportion of adverse events that were considered serious in postmenopausal women.[59,86,93] One reported events at 48 weeks,(Saag *et al.*, 1998[93]) one at 12 months,(FOSIT, Pols *et al.*, 1999[86]) and one at 24 months(Bone *et al.*, 2000[59]). One RCT in osteoporotic men reported events at 24 months.(Orwoll *et al.*, 2000[85]). Across the three RCTs in women, 205 serious AEs were observed and were similar in the alendronate groups 8.6% (103/1199) compared with placebo groups 8.7% (102/1167) (pooled RR: 0.96, 95% CI: 0.74 to 1.25, p = 0.70). The difference between treatments was not statistically significant (Figure 12). The difference between treatments was also not statistically different for men (RR: 0.80, 95% CI: 0.48 to 1.32; p=0.38). Differences between treatments were also not statistically significant by RCT duration (p = 0.46).

Figure 12: Forest plot - Any serious adverse event in alendronate compared with placebo



Seven RCTs reported on withdrawals due to AEs.(Bone *et al.*, 2000;[59] FOSIT, Pols *et al.*, 1999;[86] Orwoll *et al.*, 2000;[85] FIT I, Black *et al.*, 1996[57] FIT II, Cummings *et al.*, 1998;[66] Liberman *et al.*, 1995;[78] Saag *et al.*, 1998[93]). Across all RCTs the difference between treatments was no statistically significant [807 withdrawals; 7.8% (376/4777) in alendronate compared with 8.8% (431/4882) in placebo; pooled RR: 0.86, 95% CI: 0.73 to 1.07, p = 0.07]. No association was observed across the RCTs in postmenopausal women (Bone *et al.*, 2000;[59] FIT I, Black *et al.*, 1996[57] FIT II, Cummings *et al.*, 1998;[66] Pols *et al.*, 1999;[86] Saag *et al.*, 1998[93]) treated for 48 weeks to 48 months [793 withdrawals; 8.0% (372/4631) in alendronate compared with 8.8% (421/4787) in placebo; pooled RR: 0.90, 95% CI: 0.79 - 1.03, p = 0.13]. However, in osteoporotic men, placebo treatment was associated with higher rate of withdrawals 10.5% (10/95) compared with 2.7% (4/146) in alendronate (RR: 0.26, 95% CI: 0.08 to 0.81, p = 0.02) at 24 months,(Orwoll *et al.*, 2000;[85]) However, (Figure 13). A statistically significant difference between treatments was not evident when RCTs were pooled by RCT duration (p = 0.68).

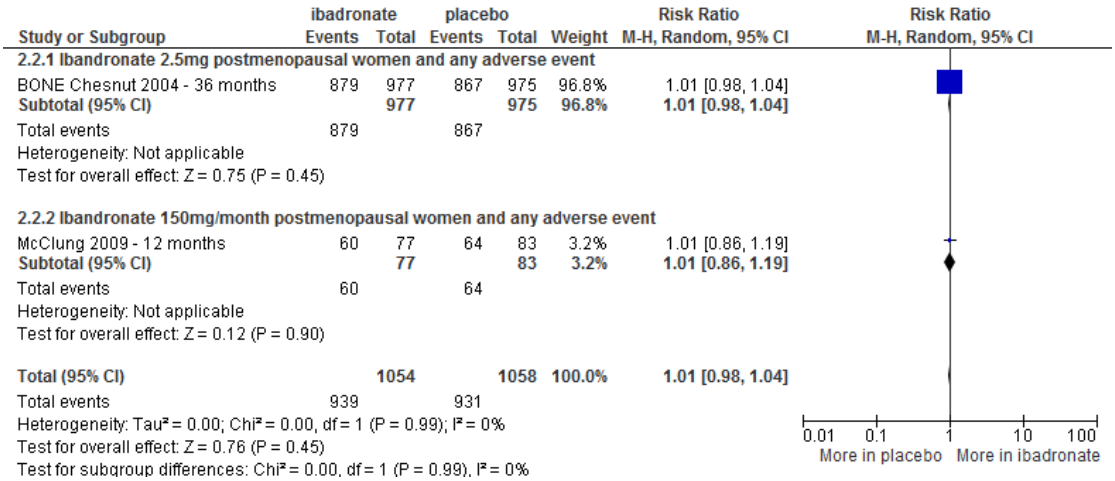
Figure 13: Forest plot - Withdrawals due to adverse event, alendronate compared with placebo



Ibandronate

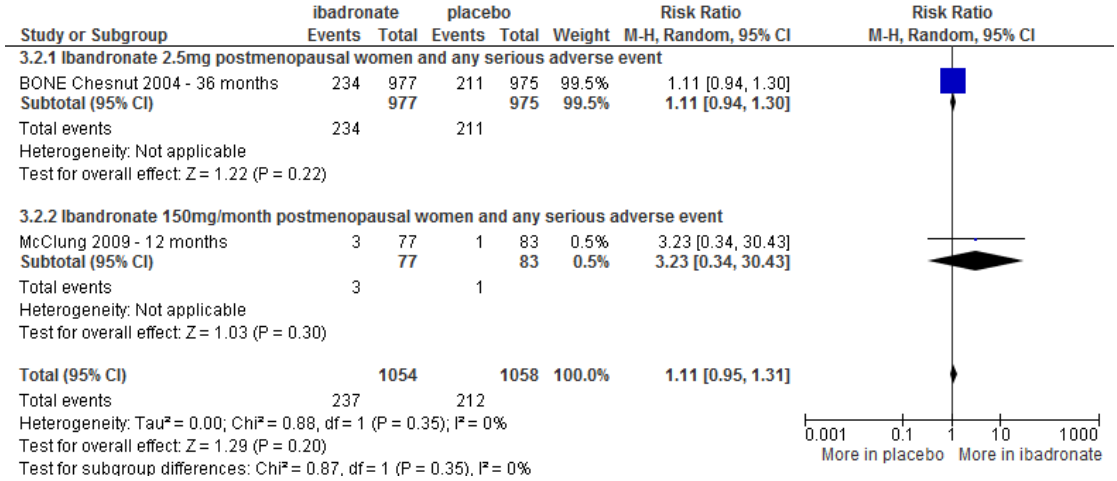
BONE, Chesnut *et al.*, 2004[45] and McClung *et al.*, 2009[82] both reported any adverse event in ibandronate compared with placebo. Both recruited postmenopausal women and follow-up was 36 and 12 months respectively. The occurrence of any adverse events did not differ by treatment group [1870 AEs; 89.9% (939/1054) in ibandronate compared with 88.0% (931/1058) in placebo; pooled RR: 1.01, 95% CI: 0.98 to 1.04, p = 0.45], and this did not vary by dosage of ibandronate (p = 0.99) (Figure 14).

Figure 14: Forest plot - Any adverse event in ibandronate compared with placebo



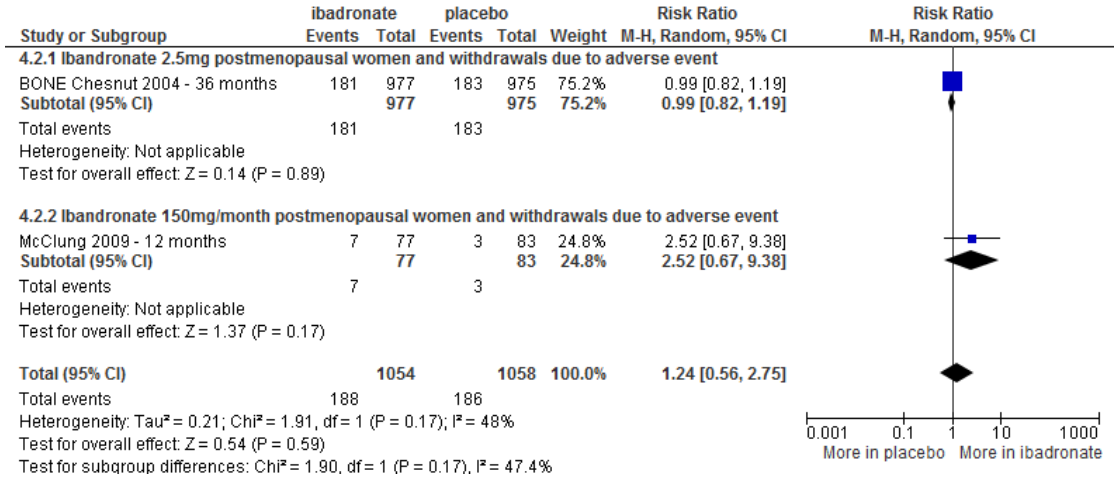
The same RCTs[45,82] also reported the number of adverse events that were considered serious. The difference between treatments across these RCTs was not statistically significant [449 serious adverse events; 22.5% (237/1054) in ibandronate compared with 20.0% (212/1058) in placebo; pooled RR: 1.11, 95% CI: 0.95 to 1.31, p = 0.20]. The difference between treatments by dose was also not statistically significant (Figure 15).

Figure 15: Forest plot - Any serious adverse event in ibandronate compared with placebo



The same RCTs also reported the number of withdrawals due to AEs.[45,82] Overall, the proportion of withdrawals in participants who were on ibandronate, 17.8% (188/1054) and placebo, 17.6% (186/1058) was similar (374 AEs; pooled RR: 1.24, 95% CI: 0.56 to 2.75, p = 0.59). The difference between treatments across these RCTs was not statistically significant, and results did not vary by ibandronate dosage (p = 0.17) (Figure 16).

Figure 16: Forest plot - Withdrawals due to adverse event in ibandronate compared with placebo

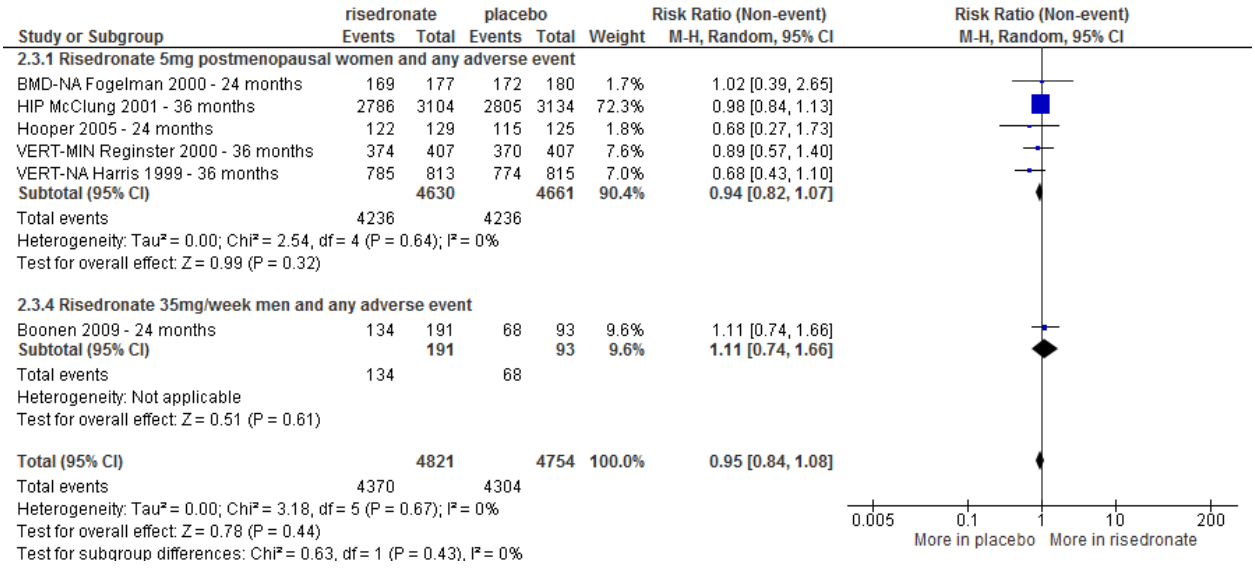


Risedronate

Six RCTs reported AEs in risedronate compared with placebo.(VERT-MN, Reginster *et al.*, 2000;[87] Hooper *et al.*, 2005[74] HIPS, McClung *et al.*, 2001;[80] VERT-NA, Harris *et al.*, 1999;[72] BMD-MN, Fogelman *et al.*, 2000;[68] Boonen *et al.*, 2009[60]) Five of these were in postmenopausal women with treatment duration from 12 to 24 months.(BMD-NA Fogelman

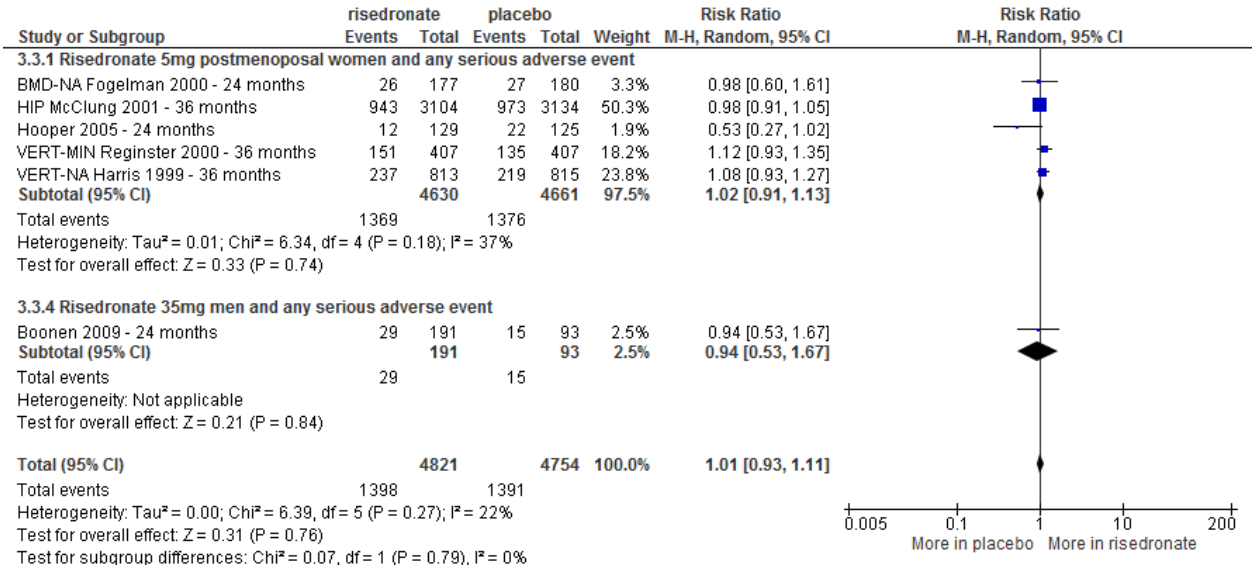
et al., 2000;[68], HIPS, McClung *et al.*, 2001;[80], VERT-MN, Reginster *et al.*, 2000;[87], VERT-NA, Harris *et al.*, 1999;[72] Hooper *et al.*, 2005[74]) One was in osteoporotic men with follow-up at 24 months.(Boonen *et al.*, 2009[60]). Pooled data across all six RCTs, (8674 AEs) showed that an equal proportion of participants on risedronate 90.6% (4370/4821) and placebo 90.5% (4304/4754) experienced an adverse event (pooled RR: 0.95, 95% CI: 0.84 to 1.08, p = 0.44). The difference between treatments was not statistically significant. The results did not vary by age, sex or dosage (p = 0.67), or duration of RCTs (p = 0.64) (Figure 17).

Figure 17: Forest plot - Any adverse event in risedronate compared with placebo



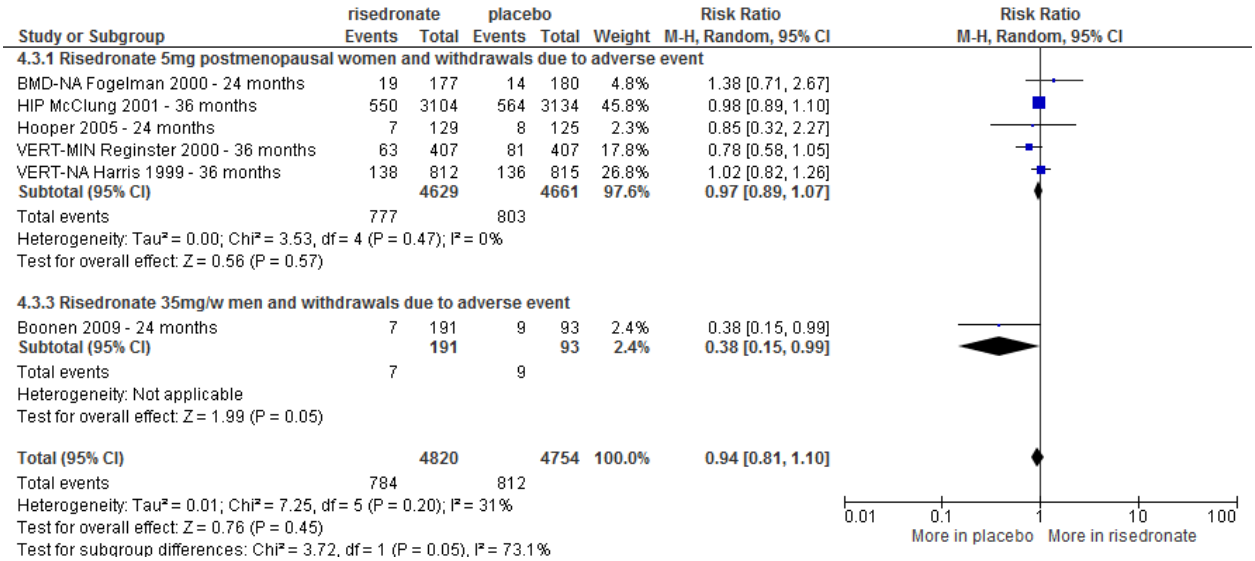
Across the same RCTs similar proportions of participants experienced serious adverse events in both treatment groups [2789 serious AEs; 29.0% (1398/4821) in risedronate compared with 29.3% (1391/4754) in placebo; pooled RR: 1.01, 95% CI: 0.93 to 1.11, p=0.76]. The difference between treatments was not statistically significant. There were no statistically significant differences between treatments evident by age, sex or dosage (p = 0.27), or treatment duration (p = 0.18) (Figure 18).

Figure 18: Forest plot - Any serious adverse event in risedronate compared with placebo



Pooled data across the six RCTs also showed there was statistically significant differences between treatments in withdrawals due to AEs [1596 withdrawals; 16.3% (784/4820) in risedronate compared with 17.1% (812/4754) in placebo; pooled RR: 0.94, 95% CI: 0.81 to 1.10, p = 0.45]. However, the difference between treatments for the one RCT in osteoporotic men with follow-up at 24 months(Boonen *et al.*, 2009[60]) was statistically significant (p=0.05) (Figure 19).

Figure 19: Forest plot - Withdrawals due to adverse event in risedronate compared with placebo

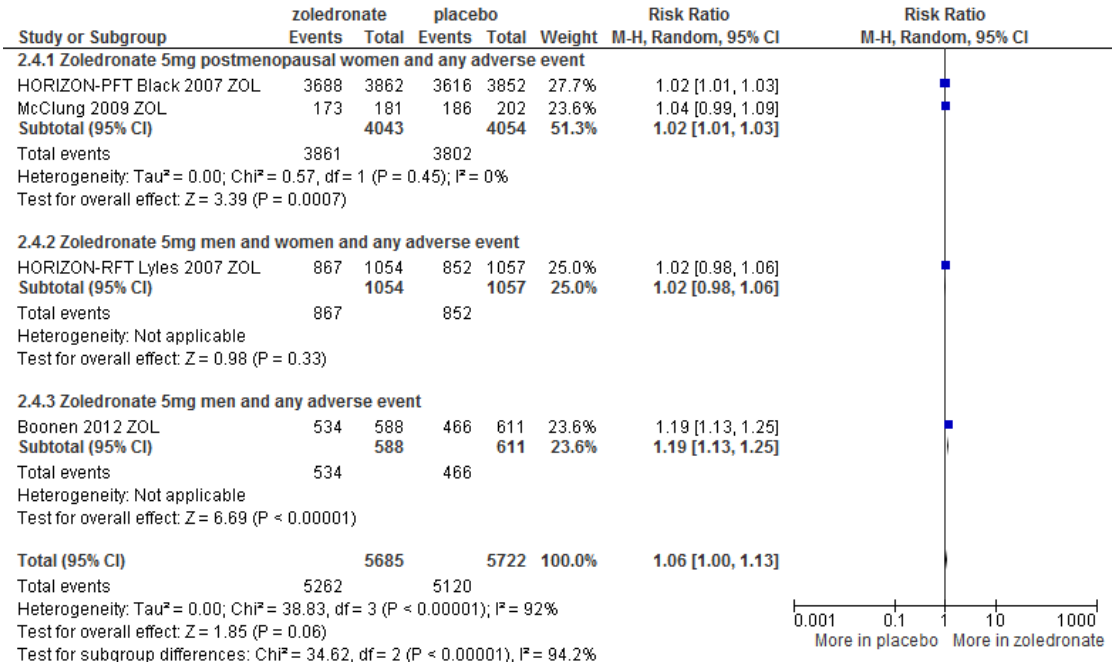


Zoledronate

Four RCTs reported AEs for zoledronate compared with placebo.(HORIZON-PFT, Black *et al.*, 1996;[58] HORIZON-RFT, Lyles *et al.*, 2007;[79] Boonen *et al.*, 2012;[61] McClung *et al.*, 2009[81]) Two evaluated followed-up postmenopausal women followed up for 36 and 24 months respectively,(HORIZON-PFT, Black *et al.*, 1996;[58] McClung *et al.*, 2009[81]) one RCT evaluated men and women with hip fracture followed up for 36 months,(HORIZON-RFT, Lyles *et al.*, 2007,[79]) One RCT evaluated osteoporotic men followed up for 36 months.(Boonen *et al.*, 2012[61])

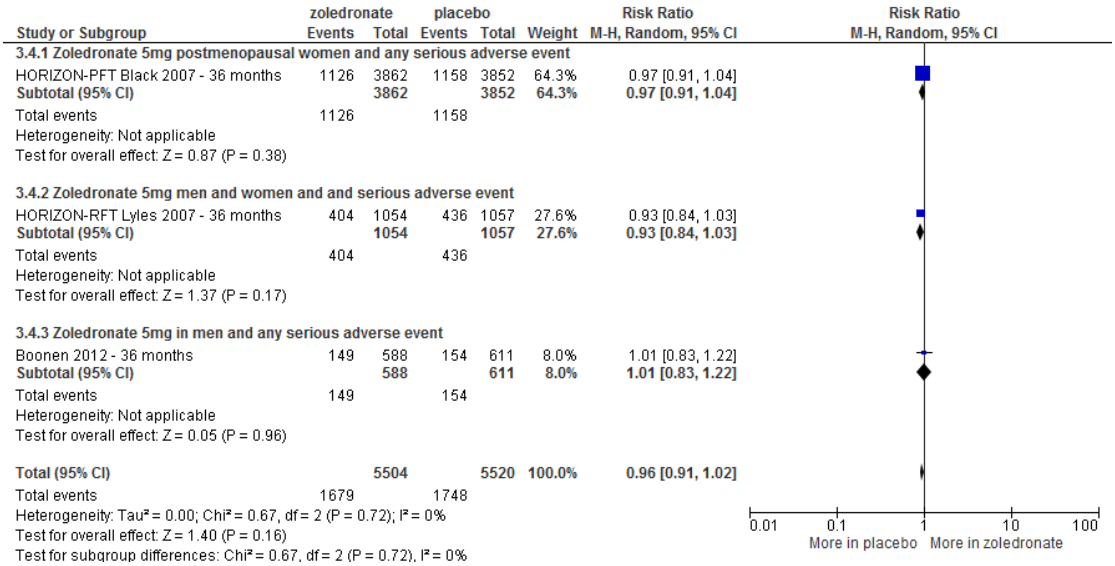
Pooled data across the two RCTs in postmenopausal women,[58,81] showed that zoledronate was associated with a statistically significant increase in incidence of adverse events [4188 AEs; 94.5% (3861/4043) in zoledronate compared with 93.8% (3802/4054) in placebo; pooled RR: 1.02, 95% CI: 1.01 to 1.03, p = 0.0007]. A 19% increase of AEs was evident from one RCT in osteoporotic men[61] [1000 AEs; 90.8% (534/588) in zoledronate compared with 76.3% (466/611) in placebo; RR: 1.19, 95% CI: 1.13 to 1.25, p = <0.00001]. The difference between treatments was statistically significant. However, the difference between treatments in one RCT in men and women was not statistically significant[79] [1719 AEs; 82.3% (867/1054) in zoledronate compared with 80.6% (852/1057) in placebo; RR: 1.02, 95% CI: 0.98 to 1.02, p = 0.33], Pooled data across all four RCTs indicated that the occurrence of AEs did not differ significantly by treatment group [10382 AEs; 92.5% (5262/5685) in zoledronate compared with 89.5% (5120/5722) in placebo; pooled RR: 1.06, 95% CI: 1.00 to 1.13, p = 0.06] (Figure 20).

Figure 20: Forest plot - Any adverse event in zoledronate compared with placebo



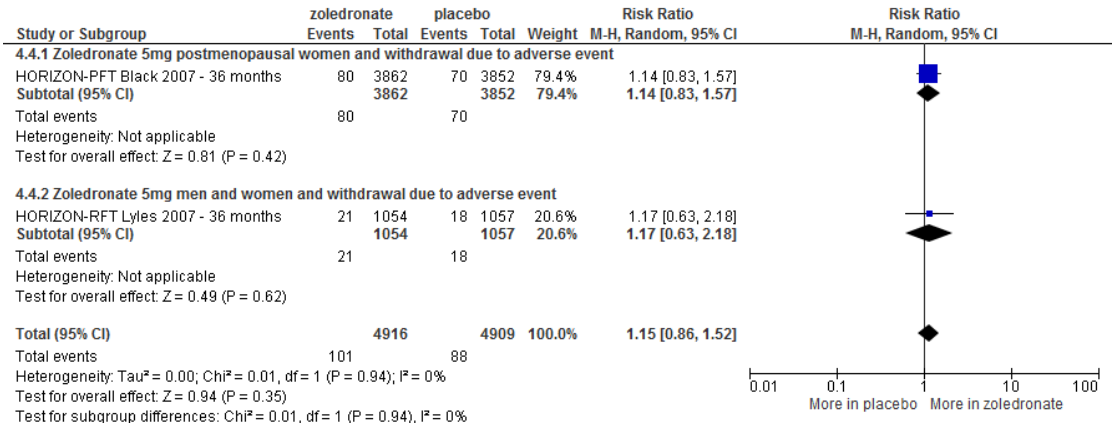
The number of serious adverse events was reported by four of the above RCTs[58,61,79,90]. Across these RCTs the difference between treatments was not statistically significant [3427 serious AEs; 30.5% (1679/5504) in zoledronate compared with 32.2% (1748/5520) in placebo; pooled RR: 0.96, 95% CI: 0.91 to 1.02, p = 0.16]. This did not differ by sex (p = 0.86), or RCT duration (p = 0.68) (Figure 21).

Figure 21: Forest plot - Any serious adverse event in zoledronate compared with placebo



Two of the above RCTs reported data on withdrawals due to AEs.[58,79] Pooled data across these RCTs showed that the rates of withdrawal were similar in the two treatment groups [189 withdrawals; 2.0% (101/4961) in zoledronate 5mg/year compared with 1.8% (88/4909) in placebo; pooled RR: 1.15, 95% CI: 0.86 to 1.52, p = 0.35]. The difference between treatments was not statistically significant. This did not differ by sex (p = 0.12). (Figure 22).

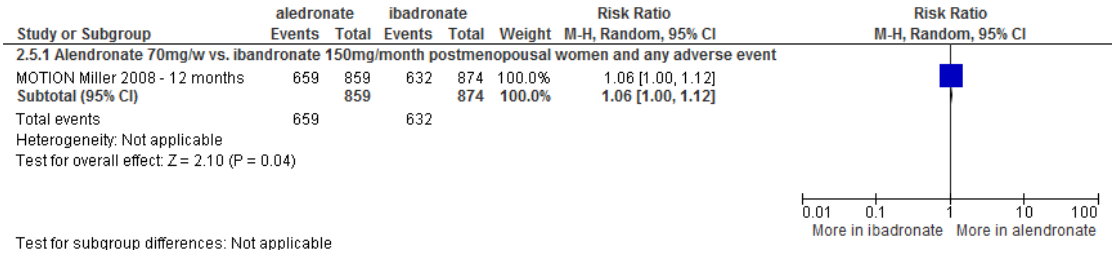
Figure 22: Forest plot - Withdrawals due to adverse event in zoledronate compared with placebo



Head to head - Alendronate *vs.* ibandronate

The MOTION trial(Miller *et al.*, 2008[83]) compared alendronate 70mg/week with ibandronate 150mg/month in postmenopausal women for 12 months. A higher proportion of adverse events were observed in participants on alendronate compared to those on ibandronate [1291 adverse events; 75.4% (659/859) in alendronate compared with 73.6% (632/874) in ibandronate; RR: 1.06, 95% CI: 1.0 to 1.12, p = 0.04]. The difference between treatments was statistically significant (Figure 23).

Figure 23: Forest plot - Alendronate compared with ibandronate and any adverse event

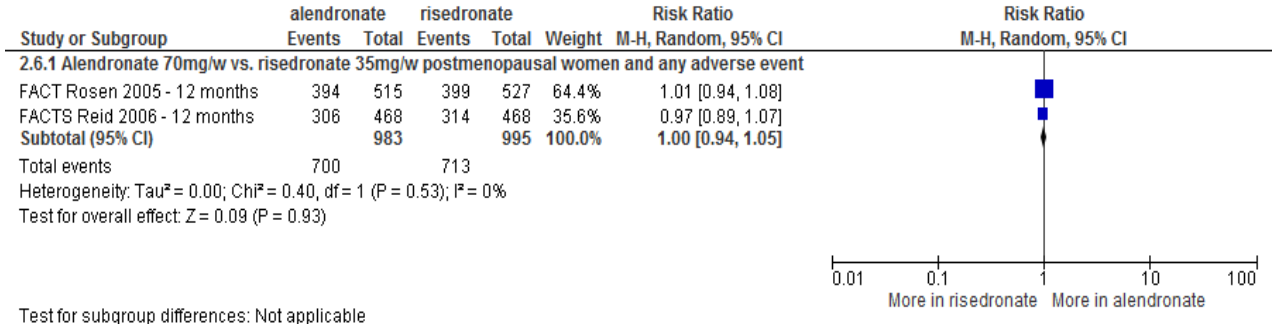


Head to head - Alendronate *vs.* risedronate

Two RCTs compared alendronate 70mg/week and risedronate 35mg/week in postmenopausal women treated for 12 months(FACT, Rosen *et al.*, 2005;[92] FACT, Reid *et al.*, 2006[89]) Pooled data across these RCTs indicate that the risk of adverse events, for the two drugs, was similar

[1413 adverse events; 71.2% (700/983) in alendronate compared with 71.7% (713/995) in risedronate; pooled RR: 1.0, 95% CI: 0.94 to 1.05, p = 0.93]. The difference between treatments was not statistically significant (Figure 24).

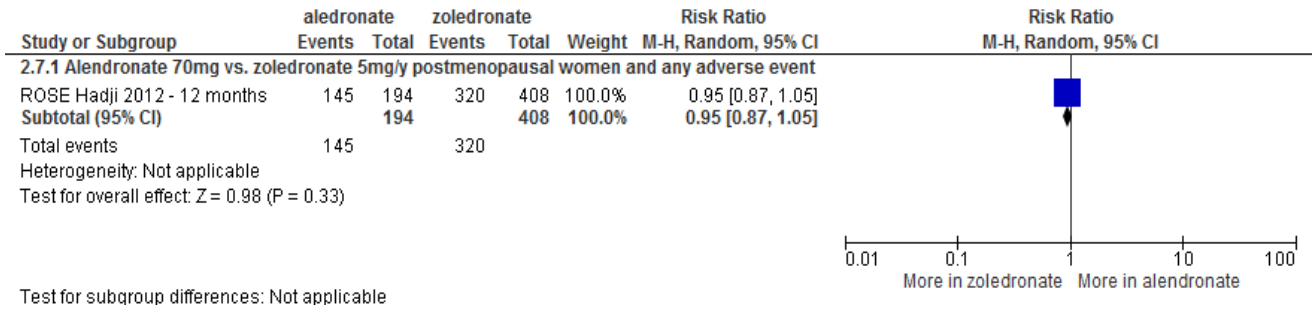
Figure 24: Forest plot - Alendronate compared with risedronate and any adverse event



Head to head - Alendronate *vs.* zoledronate

The ROSE RCT (ROSE, Hadji *et al.*, 2012[71]) compared alendronate 70mg/week compared with zoledronate 5mg/year. The risk of adverse events was similar in the two treatment groups [465 AEs; 74.7% (145/194) in alendronate compared with 78.4% (320/408) in zoledronate; RR: 0.95, 95% CI: 0.87 to 1.05, p = 0.33). The difference between treatments was not statistically significant (Figure 25).

Figure 25: Forest plot - Alendronate compared with zoledronate and any adverse event



Head-to-Head - Zoledronate compared with risedronate

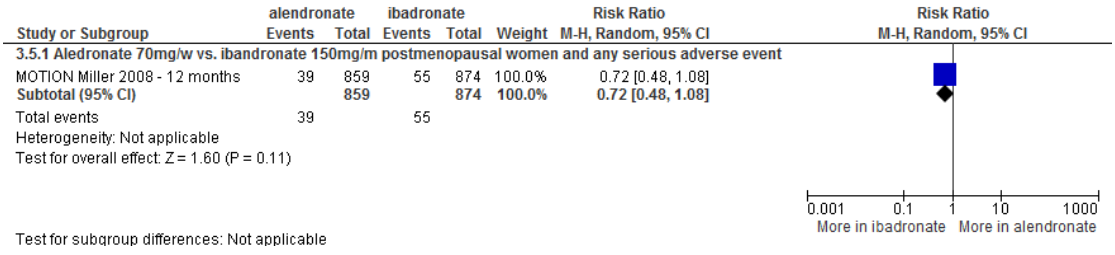
HORIZON, Reid *et al.*, 2009[90] compared zoledronate 5mg with risedronate 5mg per day in both men and women receiving steroids divided into treatment and prevention subgroups for 12 months. The difference between treatments in any adverse event in the treatment subgroup was RR 1.14 (95%CI 1.06 to 1.26, p=0.01) and the difference between treatments in the prevention subgroup was RR 1.19 (95%CI 1.03 to 1.26, p=0.01). The differences between treatments were statistically significant (more events with zoledronate). Forest plot not presented.

Serious adverse events

Head to head - Alendronate *vs.* ibandronate

The MOTION trial(MOTION, Miller *et al.*, 2008[83]) also reported the number of serious adverse events. The risk of developing serious adverse events between the two groups, was similar [94 serious AEs; 4.5% (39/859) in alendronate compared with 6.4% (55/874) in ibandronate; RR: 0.72, 95% CI: 0.48 to 1.08, p = 0.11]. The difference between treatments was not statistically significant (Figure 26).

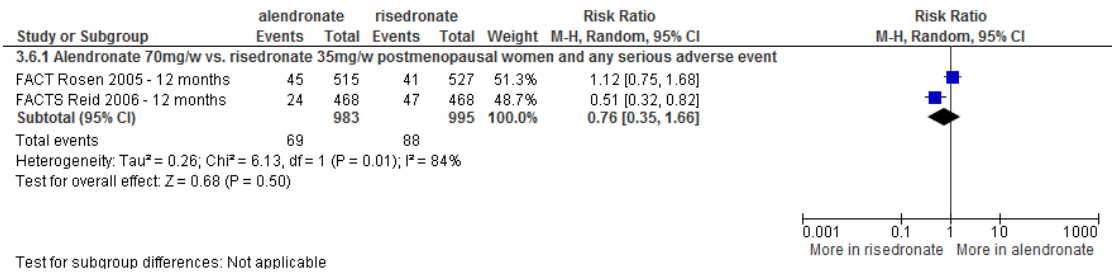
Figure 26: Forest plot - Alendronate compared with ibandronate and any serious adverse event



Head to head - Alendronate *vs.* risedronate

Pooled data across two RCTs(FACT Rosen *et al.*, 2005;[92] FACTS, Reid *et al.*, 2006[89]) indicate no statistically significant difference between treatments between the two drugs in incidence of serious adverse events [157 serious AEs; 7.0% (69/983) in alendronate compared with 8.8% (41/527) in risedronate; RR: 0.76, 95% CI: 0.35 to 1.66, p = 0.50] (Figure 27)

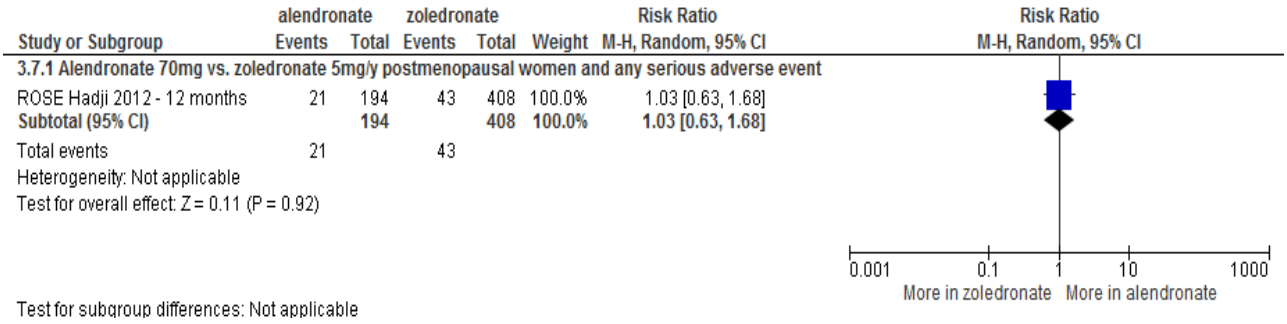
Figure 27: Forest plot - Head-to-head alendronate compared with risedronate and any serious adverse event



Head to head - Alendronate *vs.* zoledronate

The difference between treatments in the proportion of serious adverse events in alendronate 70mg/week compared with zoledronate 5mg/year was not statistically significant for one trial(ROSE trial[71]) [64 serious AEs; 10.8% (21/194) in alendronate compared with 10.5% (43/403) in zoledronate; RR: 1.03, 95% CI: 0.63 to 1.68, p = 0.92] (Figure 28).

Figure 28: Forest plot - Alendronate compared with zoledronate and any serious adverse event



Head-to-Head - Zoledronate compared with risedronate

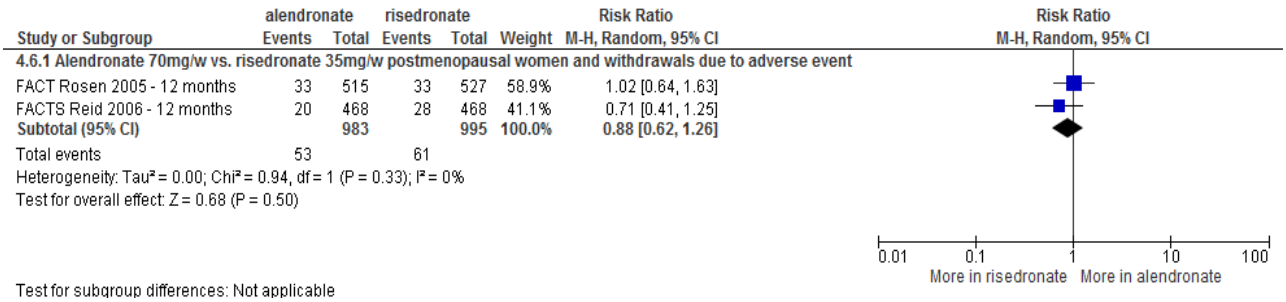
In the HORIZON, Reid *et al.*, 2009[90] where men and women receiving steroids were divided into treatment and prevention subgroups for 12 months, the difference between treatments in serious adverse events in the treatment subgroup was RR 0.93 (95%CI 0.66 to 1.31, p=0.68) and the difference between treatments in the prevention subgroup was RR 1.13 (95%CI 0.68 to 1.88, p=0.64). The differences between treatments were not statistically significant. Forest plot not presented.

Withdrawals due to adverse events

Head to head - Alendronate *vs.* risedronate

Two RCTs reported withdrawals due to adverse events(FACT Rosen *et al.*, 2005;[92] FACTS, Reid *et al.*, 2006[89]). Pooled data across these RCTs indicate no statistically significant difference between treatments [114 withdrawals; 5.4% (53/983) in alendronate compared with 6.1% (61/995) in risedronate; pooled RR: 0.88, 95% CI: 0.62 to 1.26, p = 0.50) (Figure 29).

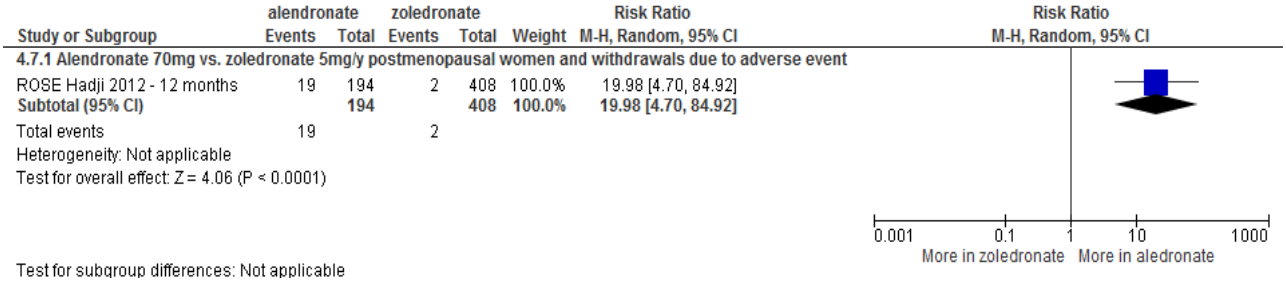
Figure 29: Forest plot - Head-to-head alendronate compared with risedronate and withdrawals due to adverse events



Head to head - Alendronate *vs.* zoledronate

The difference between treatments in withdrawals due to adverse events was statistically significant for one trial(ROSE, Hadji *et al.*, 2012 trial[71]) evaluating alendronate 70mg/week compared with zoledronate 5mg per year [21 withdrawals; 9.8% (19/194) in alendronate compared with 0.5% (2/408 in zoledronate; RR: 19.98, 95% CI: 4.70 to 84.92, p = <0.0001] (Figure 30).

Figure 30: Forest plot - Head-to-head alendronate compared with zoledronate and withdrawals due to adverse events



Head-to-Head - Zoledronate compared with risedronate

In the HORIZON, Reid *et al.*, 2009[90] where men and women receiving steroids were divided into treatment and prevention subgroups for 12 months, the difference between treatments in withdrawals due to adverse events in the treatment subgroup was RR 1.00 (95%CI 0.20 to 4.93, p=1.00) and the difference between treatments in the prevention subgroup was RR 2.00 (95%CI 0.51 to 7.84, p=0.32). The differences between treatments were not statistically significant. Forest plot not presented.

Any upper gastrointestinal (GI) adverse events

The types of upper GI events greatly varied in different RCTs. Among six RCTs[57,59,66,78,85,86] that investigated alendronate and reported specific adverse events (1738 upper GI events); abdominal pain was the most common, comprising 51.7% (557/1738) of all upper GI events followed by acid regurgitation 17.5% (304/1738), dyspepsia 11.2% (195/1738), and nausea 8.1% (140/1738). Other events included; peptic ulcers (i.e. oesophageal and stomach ulcers), gastritis, oesophagitis, belching, diarrhoea, dysphagia, constipation, heart burn, and gastroenteritis. In the six RCTs[68,72,74,80,87] administering risedronate 5mg (1076 upper GI events), abdominal pain was also the most common, comprising 43.1% (464/1076) of all upper gastrointestinal events, followed by dyspepsia, 38.9% (464/1076), oesophagitis 7.6% (82/1076) and gastritis 4.0% (43/1076). Similar results were observed in BONE trial[45], and McClung *et al.*, 2001[82], where abdominal pain and dyspepsia were the major upper GI event

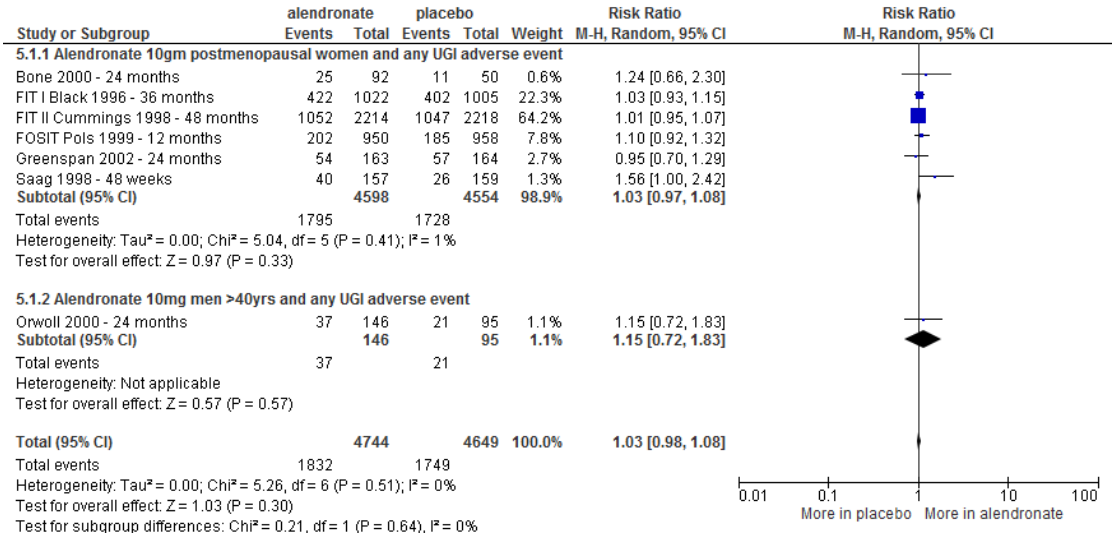
11.4% (111/977) and 31.2% (24/77) for the daily 5mg and monthly 150mg ibandronate doses respectively. Out of the 300 upper GI events occurring in participants on zoledronic 5mg in two RCTs[90,104], nausea was the major event 168 (56.0%), followed by vomiting 76 (25.3%), diarrhoea 67 (22.3%), abdominal pain 48 (16.0%), and anorexia 45 (15.0%). However, the proportion of these upper GI events was similar in treatment and in placebo except for zoledronate[104].

Alendronate

Six RCTs reporting this outcome evaluated alendronate 10mg per day in postmenopausal women.(FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] FOSIT, Pols *et al.*, 1999;[86] Bone *et al.*, 2000;[59] Greenspan *et al.*, 2002;[69] Saag *et al.*, 1998[93]) One RCT investigated alendronate 10mg in men with osteoporosis.(Orwoll *et al.*, 2000[85])

Pooled data across all seven RCTs indicated no statistically significant difference between treatments in the incidence of upper GI adverse events [3581 upper GI events; 38.6% (1832/4744) in alendronate compared with 37.6% (1749/4649) in placebo; pooled RR: 1.03, 95% CI: 0.98 to 1.08, p = 0.30] (Figure 31). There was also no statistically significant difference between treatments evident by sex (Figure 31), or RCT duration (p = 0.83).

Figure 31: Forest plot - Any upper GI adverse event, alendronate compared with placebo

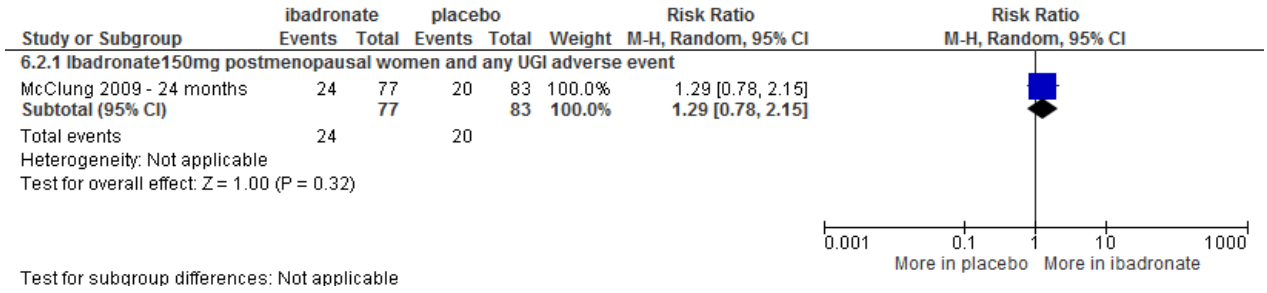


Ibandronate

Only one trial, McClung *et al.*, 2009[82] reported upper GI events. The difference between treatments was not statistically significant [44 upper GI events; 31.2% (24/77) in ibandronate

compared with 24.1% (20/83) in placebo; RR: 1.29, 95% CI: 0.78 to 2.15, p = 0.32] (Figure 32).

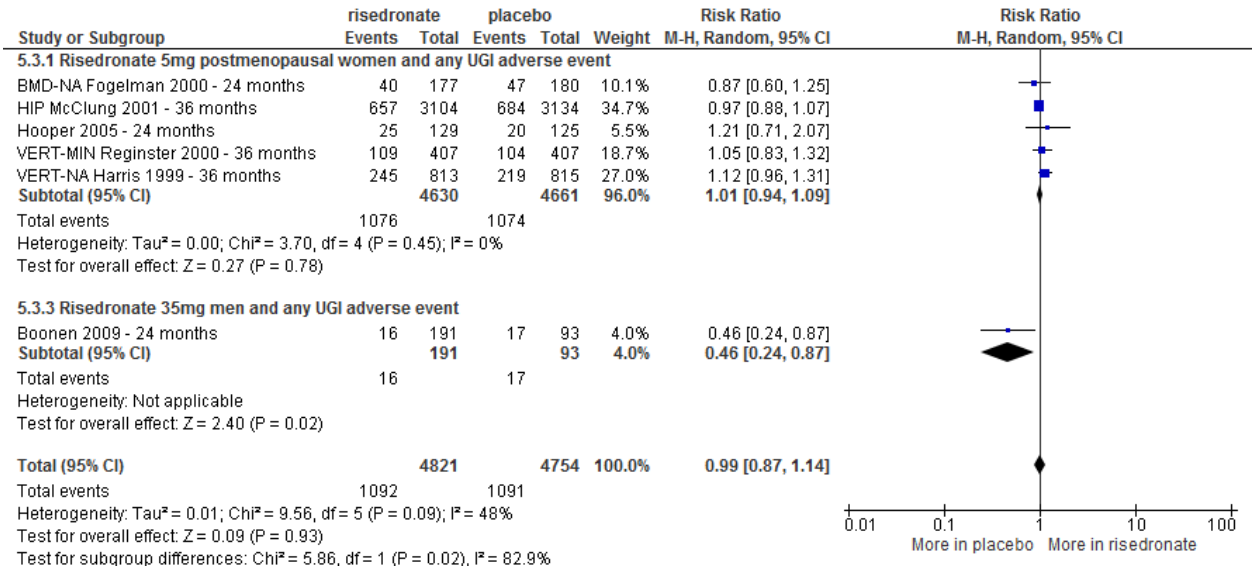
Figure 32: Forest plot - Any upper GI adverse event, ibandronate compared with placebo



Risedronate

Five RCTs evaluated risedronate 5mg/day in postmenopausal women.(VERT-MN, Reginster *et al.*, 2000;[87] VERT-NA, Harris *et al.*, 1999;[72] BMD-NA, Fogelman *et al.*, 2000;[68] Hooper *et al.*, 2005;[74] McClung *et al.*, 2001[80]) One RCT evaluated risedronate 35mg/week in osteoporotic men.(Boonen *et al.*, 2009[60]) Pooled data across the five RCTs in postmenopausal women, showed that, the overall risk of upper GI adverse events was similar in the two treatment groups [2150 upper GI events; 23.2% (1076/4630) in risedronate compared with 23.0% (1074/4661) in placebo; pooled RR: 1.04, 95% CI: 0.97 to 1.13, p = 0.75)]. The difference between treatments was not statistically significant. Pooled results across all the six RCTs showed that there was no statistically significant difference between treatments in upper GI events in risedronate or placebo [2183 upper GI events; 22.7% (1092/4821) in risedronate compared with 22.9% (1091/4754) in placebo; RR: 0.99, 95% CI: 0.87 to 1.14, p = 0.93]. This did not vary RCT duration (P = 0.45). However, in the RCT in osteoporotic men,(Boonen *et al.*, 2009[60]) the risk was significantly higher [33 upper GI events; 16/191) in risedronate compared with 19/93) in placebo; RR: 0.46, 95% CO: 0.24 to 0.87, p = 0.02] (Figure 33).

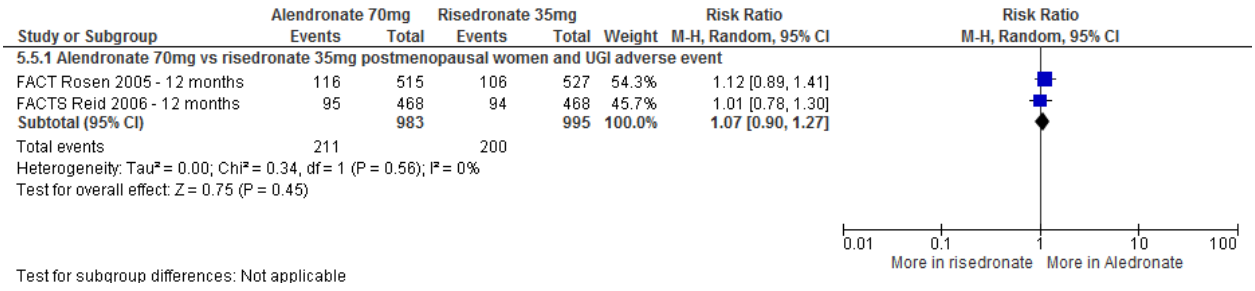
Figure 33: Forest plot - Any upper GI adverse event, risedronate compared with placebo



Alendronate *vs.* risedronate

Pooled data across two RCTs(FACT, Rosen *et al.*, 2005;[92] FACTS, Reid *et al.*, 2006[89] indicate there is no statistically significant difference between treatments in the number of upper GI events with alendronate compared with risedronate, [411 upper GI events; 21.5% (211/983) in alendronate compared with 20.1% (200/995) in risedronate; pooled RR: 1.07, 95% CI: 0.90 to 1.27, p = 0.45] (Figure 34).

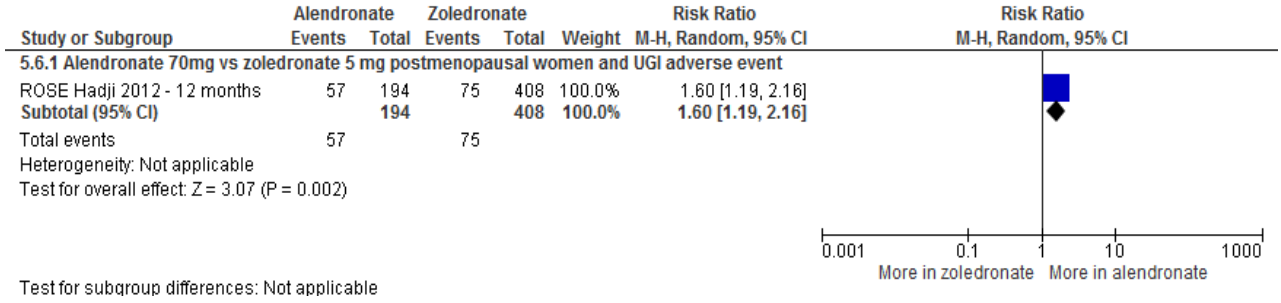
Figure 34: Forest plot - Any upper GI adverse event, alendronate compared with risedronate



Alendronate *vs.* zoledronate

The difference between treatments for one RCT reporting this outcome(ROSE, Hadji *et al.*, 2012[71]) demonstrated that a significantly higher number of upper GI events occurred in alendronate 70mg/week compared with zoledronate 5mg/year [132 upper GI events; 29.4% (57/194) in alendronate compared with 18.4% (75/408) in zoledronate; RR: 1.60, 95% CI: 1.19 to 2.16, p = 0.002] (Figure 35).

Figure 35: Forest plot - Any upper GI adverse event, alendronate compared with zoledronate



Head-to-Head - Zoledronate compared with risedronate

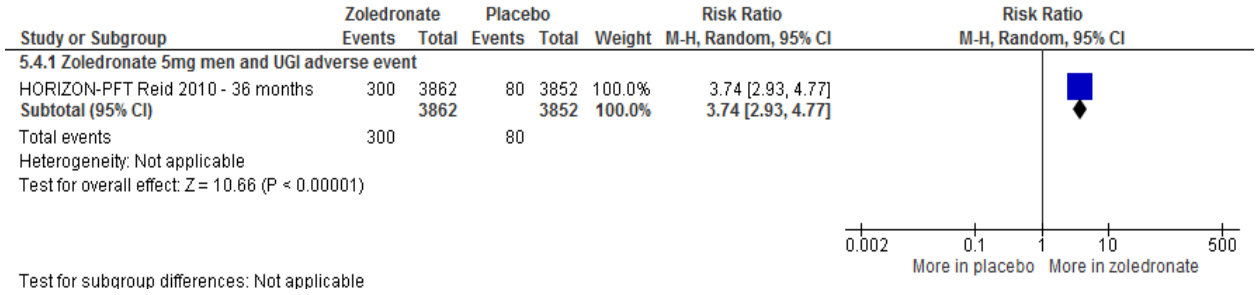
HORIZON, Reid *et al.*, 2009[90] compared zoledronate 5mg with risedronate 5mg per day in both men and women receiving steroids divided into treatment and prevention subgroups for 12 months. The p-values for the differences between treatments in upper GI adverse events reported between the treatment subgroup were: upper abdominal pain, p=0.158; abdominal pain, p=0.16; dyspepsia, p=0.70; nausea, p=0.19; vomiting, p=0.04; gastritis, p=0.68; gastro-oesophageal reflux, 0.37. The p-values for the differences between treatments reported between the prevention subgroup were: upper abdominal pain, p=1.00; abdominal pain, p=1.00; dyspepsia, p=0.57; nausea, p=0.52; vomiting, p=1.00; gastritis, p=1.00; gastro-oesophageal reflux, 0.44.

Any gastrointestinal event

Zoledronate

A significantly higher proportion of any GI event (abdominal pain, anorexia, diarrohea, nausea, vomiting) in the first three days following i.v. administration in participants on zoledronate compared with those on placebo was reported by HORIZON-PFT, Reid *et al.* (2010)[104] [380 GI events; 7.8% (300/3862) in zoledronate compared with 2.1% (80/3852 in placebo; RR: 3.74, 95% CI: 2.93 to 4.77, p = <0.00001] (Figure 36).

Figure 36: Forest plot - Any GI adverse event, zoledronate compared with placebo



Influenza-like symptoms

The reporting of influenza-like symptoms varied across RCT including; upper respiratory infections, influenza, pyrexia, headache, chills, nasopharyngitis, bronchitis, pneumonia, cough and fatigue. Some RCTs only reported the occurrence of influenza-type symptoms, whereas others documented a number of potentially associated symptoms.

Alendronate

One RCT in osteoporotic men reported on influenza-like symptoms.(Orwoll *et al.*, 2000[85]). The occurrence was similar in alendronate and in placebo [113 influenza-like symptoms; 45.2% (66/146) in alendronate compared with 49.5% (47/95) in placebo; RR: 0.91, 95% CI: 0.70 to 1.20, p = 0.51)]. The difference between treatments was not statistically significant.

Ibandronate

In the RCT by McClung *et al.*, 2009,[82], 5.2% (4/83) of participants on ibandronate 150mg/month developed influenza-like symptoms whilst none of the 83 (0%) participants on placebo developed symptoms. The difference between treatments was not statistically significant (p = 0.12).

Risedronate

Boonen 2009[60] reported the number of participants on risedronate 35mg/week and placebo who developed influenza, and nasopharyngitis. The differences between treatments in these outcomes were not statistically significant [[15 influenza cases; 5.8% (11/191) in risedronate 35mg/week compared with 5.4% (5/93) in placebo; RR: 1.07, 95% CI: 0.38 to 2.99, p = 0.90], and 15 nasopharyngitis cases; 5.8% (11/191) in risedronate 35mg/week compared with 5.4% (5/93) in placebo; RR: 1.07, 95% CI: 0.38 to 2.99, p = 0.90]].

Zoledronate

Five included RCTs reported on influenza-like symptoms.(Boonen *et al.*, 2012;[61] McClung *et al.*, 2009;[81] HORIZON, Reid *et al.*, 2009;[90] HORIZON-RFT, Lyles *et al.*, 2007;[79] HORIZON-PFT, Black *et al.*, 2007[58])

Across these RCTs statistically significant differences between treatments associated with zoledronate were evident for: pyrexia [1048 cases; 15.2% (907/5957) in zoledronate compared with 2.4% (141/5866) in placebo; pooled RR: 4.36, 95% CI: 1.91 to 9.98, p = <0.0005] (Figure 37); headache [554 cases; 8.3% (405/4903) in zoledronate compared with 3.1% (149/4809) in placebo; pooled RR: 2.14, 95% CI: 1.36 to 3.39, p = 0.001] (Figure 38);

and chills [53 cases; 9.7% (44/453) in zoledronate compared with 2.6%(9/346) in placebo; pooled RR: 3.81, 95% CI: 1.25 to 11.60, p<0.02] (Figure 39). The occurrence of pyrexia, and headache significantly differed by sex (p<0.00001, p = 0.004).

Figure 37: Forest plot - Zoledronate compared with placebo, pyrexia

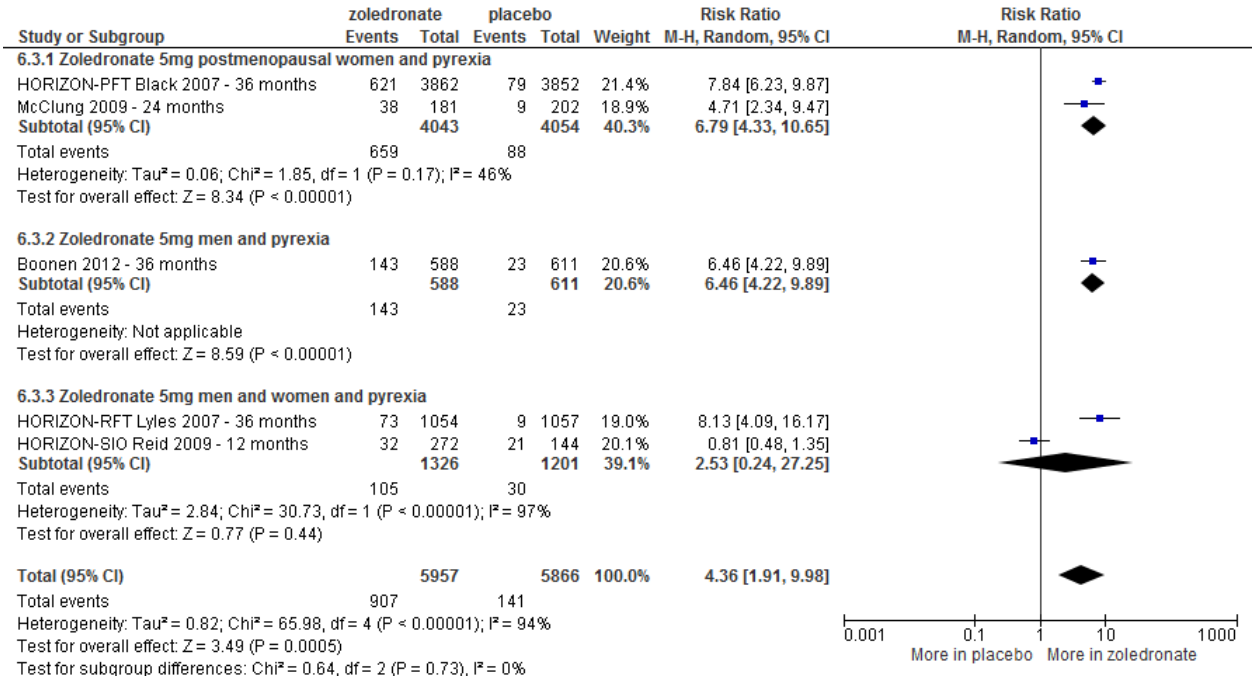


Figure 38: Forest plot - Zoledronate compared with placebo, headache

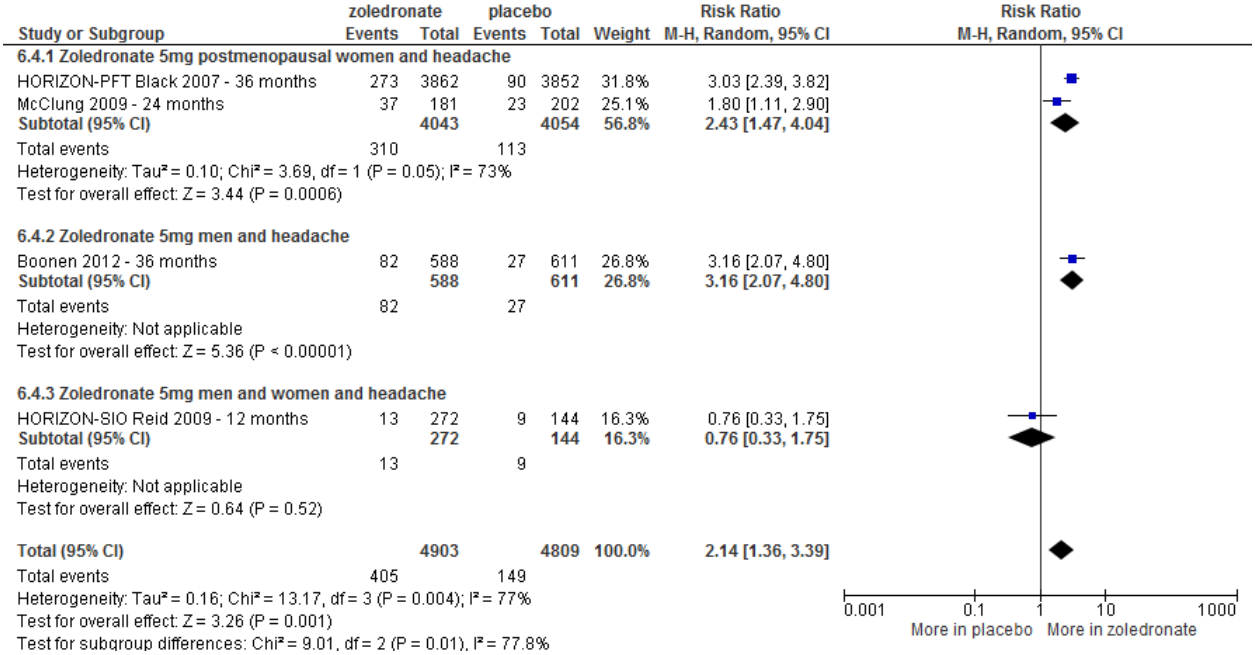
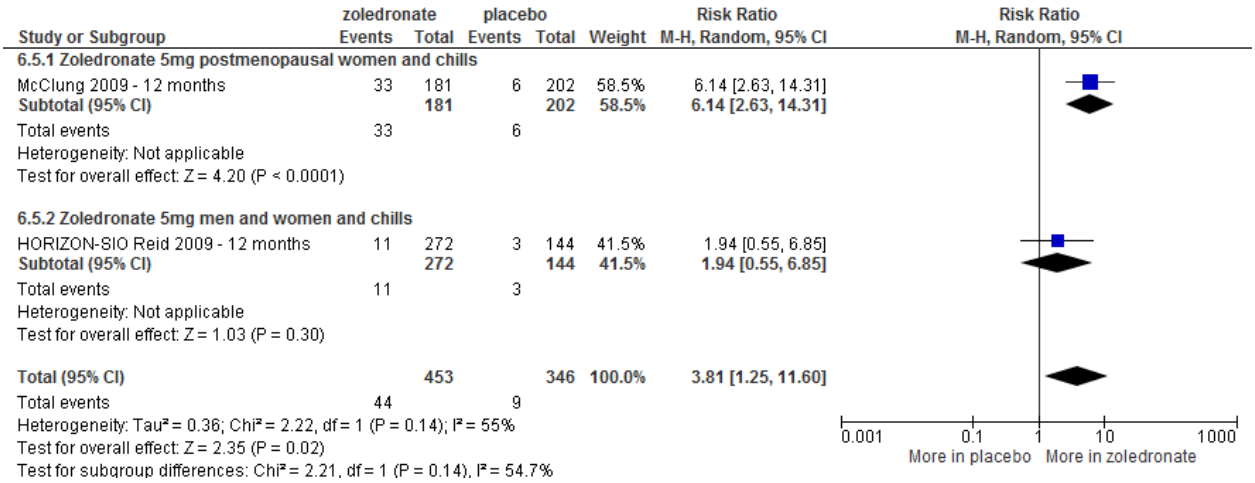


Figure 39: Forest plot - Zoledronate compared with placebo, chills



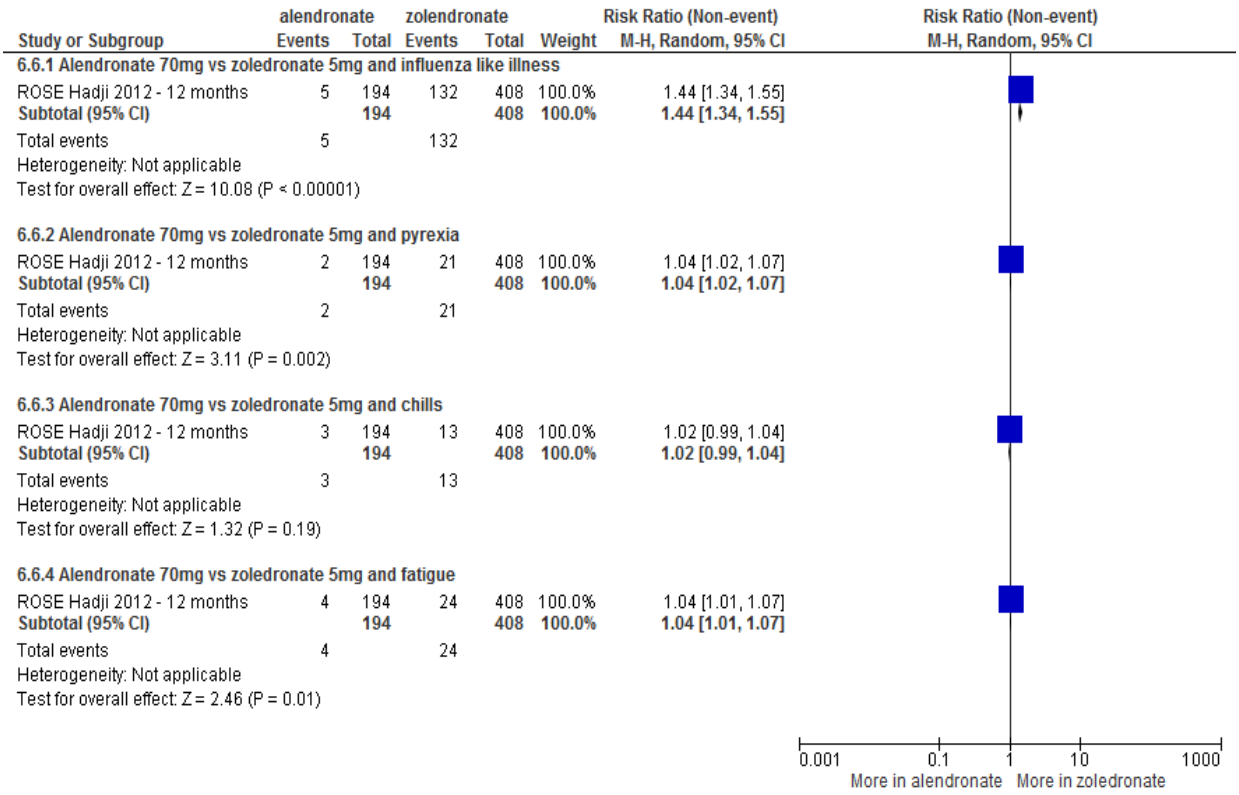
Alendronate *vs.* ibandronate

There were no statistically significant differences between treatments evident from one trial(MOTION, Miller *et al.*, 2008[83]) in in either influenza [influenza 85 events; 4.2% (36/859) in alendronate compared with 5.6% (49/874) in ibandronate; RR: 0.75, 95% CI: 0.49 to 1.14, p = 0.17], or nasopharyngitis [92 cases; 4.8% (41/859) in alendronate compared with 5.8% (51/874) in ibandronate; RR: 0.82, 95% CI: 0.55 to 1.22, p = 0.33]

Alendronate *vs.* zoledronate

The differences between treatments evident from the ROSE trial[71] demonstrated that zoledronate 5mg was associated with significantly more influenza-like symptoms compared to alendronate 70mg [137 cases; 2.6% (5/194) in alendronate compared with 32.4% (132/408) in zoledronate; RR: 1.44, 95% CI: 1.34 to 1.55, p = <0.00001]; slight increase in pyrexia [23 cases; 1.0% (2/194) in alendronate compared with 5.2% (21/408) in zoledronate; RR: 1.04, 95% CI: 1.02 to 1.07, p = 0.002] and fatigue [28 cases; 2.1% (4/194) in alendronate compared with 5.9% (24/408) in zoledronate; RR: 1.04, 95% CI: 1.01 to 1.07, p = 0.01] (Figure 40).

Figure 40: Forest plot - Alendronate 70mg compared with zoledronate 5mg/year, Influenza-like symptoms



Head-to-Head - Zoledronate compared with risedronate

HORIZON, Reid *et al.*, 2009[90] compared zoledronate 5mg with risedronate 5mg per day in both men and women receiving steroids divided into treatment and prevention subgroups for 12 months. The difference between treatments in influenza-like symptoms in the treatment subgroup was RR 5.02 (95%CI 1.47 to 17.14, p=0.01) and the difference between treatments in the prevention subgroup was RR 10.00 (95%CI 1.30 to 77.09, p=0.03). The differences between treatments were statistically significant (more events with zoledronate). Forest plot not presented.

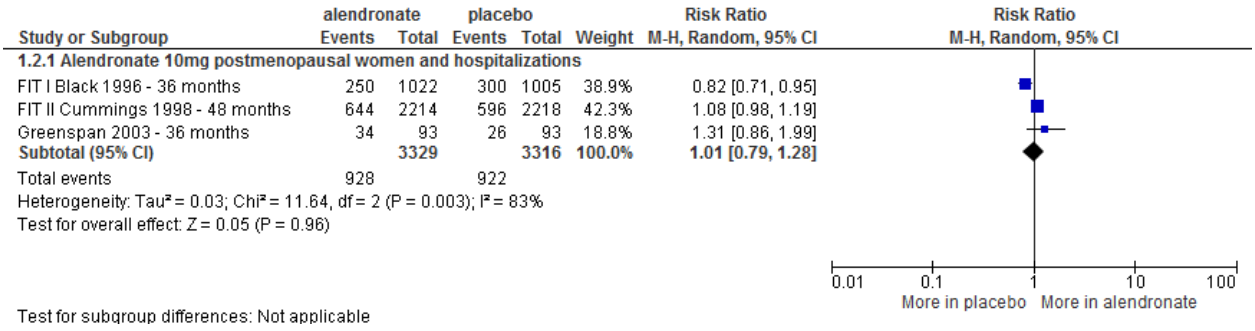
Risk of hospitalisation

Alendronate

Three RCTs in postmenopausal women reported on hospitalisation (FIT I, Black *et al.*, 1996;[57] FIT II, Cummings *et al.*, 1998;[66] Greenspan *et al.*, 2003[70]). A total number of 1855 participants were hospitalised during 36 months[57,70] and 48 months of follow-up[66]. Across these RCTs there was no statistically significant difference between treatments in the risk of hospitalisation between participants receiving alendronate 27.9% (928/3329) compared with

27.8% (922/3316) among those on placebo (pooled RR: 1.01, 95% CI: 0.79 to 1.28, p = 0.96) (Figure 41).

Figure 41: Forest plot for Hospitalisation in postmenopausal women on alendronate 10mg compared with placebo



ARCT fibrillation

ARCT fibrillation was reported as an adverse event outcome across the two HORIZON RCTs evaluating zoledronate compared with placebo (HORIZON-PFT, Black et al., 2007;[58] HORIZON-RFT, Lyles *et al.,* 2007[79]) and the HORIZON RCT in men and women receiving glucocorticoids (HORIZON, Reid et al., 2009[90]) (Appendix 5). Across these RCTs no statistically significant differences between treatments were evident. (HORIZON-PFT, RR 1.28 [95%CI 0.95 to 1.74], p=0.10; HORIZON-RFT, RR 1.21 [95%CI 0.80 to 1.85], p=0.37; HORIZON glucocorticoid - prevention group, RR 7.00 [95%CI 0.36 to 134.31], p=0.20; HORIZON glucocorticoid - prevention group, zero events in both arms). Forest plots not presented.

Bone pain

Bone pain was reported as an adverse event outcome by two RCTs.[71,90]

Head-to-Head - Zoledronate compared with risedronate

HORIZON, Reid *et al.*, 2009[90] compared zoledronate 5mg with risedronate 5mg per day in both men and women receiving steroids divided into treatment and prevention subgroups for 12 months. The difference between treatments in bone pain in the treatment subgroup was RR 2.61 (95%CI 0.94 to 7.22, p=0.06). The difference between treatments was not statistically significant. There were zero events in both arms of the prevention subgroup. Forest plot not presented.

Head-to-Head - Alendronate compared with zoledronate

The ROSE RCT (ROSE, Hadji *et al.*, 2012[71]) compared alendronate 70mg/week compared with zoledronate 5mg/year. The difference between treatments in bone pain was RR 6.91 (95%CI 3.02 to 15.83, p<0.00001). The difference between treatments was statistically significant (more events with zoledronate). Forest plot not presented. There were zero events in both arms of the prevention subgroup.

Conjunctivitis

Zoledronate

The HORIZON-PFT RCT (Reid *et al.*, 2010[104]) reported on eye inflammation as an adverse event in the first three days following administration of i.v. zoledronate 5mg or placebo in osteoporotic women. The difference between treatments in eye inflammation was RR 6.98 (95%CI 1.59 to 30.70, p=0.01). The difference between treatments was statistically significant (more events with zoledronate). Forest plot not presented.

Stroke

Zoledronate

The HORIZON-RFT RCT (Lyles *et al.*, 2007[79]) reported on stroke as an adverse event in men and women following hip fracture receiving zoledronate 5mg or placebo over . The difference between treatments in stroke was RR 1.21 (95%CI 0.80 to 1.85, p=0.37). The difference between treatments was not statistically significant. Forest plot not presented.

Osteonecrosis of the jaw,

Zoledronate

Four placebo-controlled RCTs evaluating zoledronate,(HORIZON-PFT, Black *et al.,* 2007;[58] HORIZON-RFT, Lyles *et al.,* 2007;[79] Boonen *et al.,* 2012;[61] McClung *et al.,* 2009[81]) one RCT comparing zoledronate with risedronate (HORIZON, Reid *et al.,* 2009[90]) and one RCT comparing zoledronate with alendronate (ROSE, Hadji *et al.*, 2012[71]) all reported that no cases of spontaneous osteonecrosis were observed during the RCT period. The HORIZON-PFT RCT (Black *et al.,* 2007[58]) reported that cases of osteonecrosis in both the zoledronate and placebo groups following dental surgery (one case in each group) resolved with antibiotic therapy.

Hypocalcaemia and atypical femoral fracture,

None of the included RCTs reported on these adverse event outcomes.

Systematic review evidence for adverse events

A supplementary search in Medline (Ovid) and Embase (Ovid) for systematic reviews reporting on adverse effects of treatment was undertaken on 6 January 2015. Keywords and subheading for adverse events and safety with the drug names and a reviews search filter. The Medline search strategy is presented in Appendix 2. One hundred seventy additional citations were identified. These records were sifted by a single reviewer (FC). Fourteen reviews were identified that summarised evidence for adverse events across studies in bisphosphonates. A summary of these reviews and their findings is presented in Appendix 6.

Any adverse event / upper GI events

The review by Bobba *et al.* (2006)[120] evaluated the evidence from 14 studies in alendronate, eight studies in risedronate, ten studies in ibandronate and nine studies in zoledronate. RCTs and observational studies were included. Across the evidence base, the reviewers summarised that alendronate, risedronate and oral ibandronate have similar rates of GI toxicity when compared with placebo. In addition, no significant difference in renal toxicity was evident for i.v. ibandronate compared with placebo. However, a decrease in renal function was evident with zoledronate. Osteonecrosis of the jaw was rarely described in participants receiving oral bisphosphonates. More commonly osteonecrosis of the jaw was reported in participants with malignancy receiving zoledronate. The authors concluded that the adverse events associated with alendronate, risedronate and oral ibandronate are minimal. However, zoledronate may be compromised by renal toxicity. Myalgias and arthralgias were evident in the acute phase following i.v. administration.

In a review of clinical efficacy of risedronate for postmenopausal osteoporosis, Paget's disease, participants with breast cancer and participants taking glucocorticoids, Crandall (2001)[121] evaluated the evidence across nine RCTs and seven clinical trials. The author summarised that across six RCTs of risedronate for any condition, safety data indicated that risedronate is similar to placebo and does not include any notable upper GI adverse event rate.

In a comparative review of pivotal trials of alendronate and risedronate including a meta-analysis, Kherani, Papaioannou and Adachi (2002)[122] concluded that both alendronate and risedronate studies demonstrate similar adverse event rates between placebo and active treatment.

In a review of clinical studies and review articles concerning the use of risedronate, Umland and Boyce (2001)[123] observed that although postmarketing surveillance studies reported an increase in serious or severe upper gastrointestinal side effects with alendronate, similar findings were not evident for risedronate. The reviewers concluded that risedronate has been associated with a lower incidence of gastric ulcers than alendronate. However, adverse events associated with risedronate are generally comparable to those observed with placebo in most clinical trials.

As part of a NICE report on adverse effects and persistence with oral bisphosphonates, Lloyd-Jones and Wilkinson (2006)[124] reported that across UK prescription event monitoring studies treatment with daily alendronate or risedronate is associated with a high level of reporting of a number of conditions in the first month of therapy, particularly those affecting the upper gastrointestinal tract: there were around 30 reports of dyspepsia, the most commonly reported condition, per 1000 patient-months of exposure. However, RCTs of tolerability found no increased incidence of adverse events in patients randomised to alendronate.

The Atavis submission for this assessment reported that patients switched from risedronate to alendronate have shown a significant increase in the risk of GI side effects. In a retrospective cohort study evaluating anonymous medical records from 390 general practices in the UK, Ralston *et al.*, 2010[125] reported that the risk of developing a GI adverse event was higher in patients who switched to alendronate compared with those who remained on risedronate (hazard ratio, 1.85; 95%CI 1.26 to 2.72). The authors also reported that the risk was even greater in the subgroup of patients with a history of upper GI events (HR, 3.18; 95%CI 2.79 to 3.63) but was also observed in patients with no history of GI events (HR, 1.76; 95%CI 1.15 to 2.69). The authors concluded that switching patients who are stabilized on risedronate to alendronate is associated with an increased risk of GI adverse effects.

Osteonecrosis of the jaw

In a review specifically of bisphosphonate-induced osteonecrosis of the jaw, Krueger *et al.* (2007)[126] reviewed the evidence from 11 case reports and 26 case series studies reporting actual cases linking osteonecrosis of the jaw with bisphosphonate use, the majority of which reported on zoledronate. The reviewers summarised that from the available literature intravenous bisphosphonates, especially zoledronate, are more likely to predispose patients to osteonecrosis of the jaw. However, in addition to bisphosphonate use, there appear to be several other factors involved in the development of osteonecrosis of the jaw. Other risk factors noted from the included studies were dental extraction or trauma to the jaw exposing part of the bone.

Van den Wyngaert, Huizing and Vermorken (2006)[127] also reviewed the evidence for bisphosphonates and osteonecrosis of the jaw across 22 studies based on retrospective chart reviews without control, of which three included patients with osteoporosis. Zoledronate and pamidronate were the main bisphosphonates covered. The reviewers observed that across the studies, 69.3% of patients had undergone a dental extraction prior to the development of osteonecrosis, concluding that this would confirm the importance of trauma in the initiation of the disease. However, not enough evidence is available to prove a causal link.

Woo, Hellstein and Kalmar (2006)[128] also reviewed the evidence for bisphosphonates and osteonecrosis of the jaw across 29 case reports. Zoledronate, aledronate and pamidronate were the main bisphosphonates covered. Across the included reports, 94% of patients were treated with zoledronate or pamidronate or both; 85% of affected patients had multiple myeloma or metastatic breast cancer, and 4% had osteoporosis. The reviewers concluded that the prevalence of osteonecrosis in patients with cancer is 6% to 10% and the prevalence in those taking alendronate for osteoporosis is unknown. The authors also concluded that more than half of all cases (60%) occur after dentoalveolar surgery (such as tooth extraction) to treat infections, and the remaining 40% are probably related to infection, denture trauma, or other physical trauma.

Recently, Lee *et al.* (2014)[129] have undertaken a meta-analysis across 12 cohort and case-control studies evaluating oral and i.v. administered bishphosphonates. An inclusion criterion was studies in non-cancer patients. The pooled effect estimate indicated that the use of bisphosphonates was associated with a significantly increased risk of jaw osteonecrosis (odds ratio 2.32; 95% CI 1.38 to3.91). The reviewers concluded that that use of bisphosphonates in non-cancer patients is associated with a substantial risk for jaw osteonecrosis and that patients receiving i.v. bisphosphonates are at highest risk.

Atypical fracture

Giusti, Hamdy and Papapoulos (2010)[130] reviewed the evidence across 39 publications in women treated with a bisphosphonate at a dosing regimen used for the prevention or treatment of osteoporosis:. Twenty-seven publications were case series or case reports (one abstract), four were retrospective studies and one was a prospective article including three new cases. In most cases, the bisphosphonate was alendronate, prescribed for prevention or treatment of osteoporosis. Across the included studies the reviewers summarised that there were 58 femoral shaft fractures and 41 subtrochanteric fractures; the precise fracture site was not specified in 42 cases. Nineteen fractures were diagnosed at presentation as insufficiency fractures, with 12 of these progressing to a complete fracture. Overall, 53 (44.2%) of the 120

patients with available data had a contralateral fracture (32 of which were insufficiency fractures), either concurrently or subsequently to the initial fracture, 34 (64.2%) of which occurred in the same anatomical location as the first fracture. The reviewers concluded that the analysis allowed the clinical identification of patients at risk of developing atypical fractures. However, that long-term bisphosphonate therapy is not a prerequisite for development of atypical fractures. Moreover, the use of glucocorticoids and proton pump inhibitors are important risk factors for atypical fracture.

Recently, Gedmintas, Solomon and Kim (2013)[131] have undertaken a meta-analysis of atypical fractures across five case-control and six cohort studies. The studies were mainly in women and evaluated mainly alendronate but also ibandronate, risedronate, zoledronate and other bisphosphonates. The overall pooled estimate for atypical fractures associated with bisphosphonates using data from the five case-control and six cohort studies was (RR) 1.70 (95%CI, 1.22 to 2.37). The reviewers concluded that the meta-analysis suggests there is an increased risk of atypical fracture among bisphosphonate users. However, that atypical fractures are rare events even in bisphosphonate users.

Oesophageal cancer

Andrici, Tio and Eslick (2012)[132] undertook a meta-analysis investigating oral bisphosphonates and the risk of oesophageal cancer. Seven cohort or case-control studies were included. Patients were any who had filed a prescription for any antiresorptive drug. The authors obversed found a positive relationship between exposure to bisphosphonates and oesophageal cancer, with an odds ratio of 1.74 (95%CI, 1.19 to2.55). An increased risk of oesophageal cancer was also found in the group exposed to bisphosphonates for a longer period of time. The reviewers summarised that the results suggest a possible association between oral bisphosphonates and oesophageal cancer, which was increased with a longer exposure period. An increased risk was observed for etidronate, but not alendronate.

Recently, Sun *et al.* (2013)[133] undertook a a meta-analysis of observational studies. Seven epidemiologic studies that consisted of four cohort studies and three case control studies were included. Where reported, alendronate was the main bisphosphonate. The underlying conditions for which patients were being treated with bisphosphonate in the included studies was not reported. In the primary analysis, bisphosphonate treatment was not associated with risk of oesophageal cancer in both cohort studies (pooled relative risk RR 1.23 [95%CI 0.79 to 1.92]) and case control studies, pooled odds ratio 1.24 (95%CI 0.98 to 1.57). The reviewers also observed no significant increased risk of esophageal cancer in alendronate users alone across cohort studies (RR 1.08, 95%CI 0.67 to 1.75), or across case control

studies (OR 1.16, 95%CI 0.82 to 1.63]). The reviewers concluded that bisphosphonate treatment was not significantly associated with excess risk of esophageal cancer.

Atrial fibrillation

Loke, Jeevanantham and Singh (2009)[134], evaluated the risk of atrial fibrillation associated with biphosphonate use in patients with osteoporosis or fractures. RCTs of any biphosphonate compared to placebo, or case control and prospective or retrospective cohort studies in patients with osteoporosis that reported on the association between biphosphonate exposure and atrial fibrillation were eligible for inclusion. Interventions in the included RCTs included, alendronate, risedronate or zoledronate. Interventions in the included case control studies were mostly alendronate or etidronate. Across nine RCTs biphosphonates significantly increased the risk of serious adverse events for atrial fibrillation compared to placebo (OR 1.47, 95% CI 1.01 to 2.14; nine RCTs). Biphosphonates did not significantly increase risk of stroke or cardiovascular mortality (three RCTs). One case-control study found that patients with atrial fibrillation were more likely to have used biphosphonates than control patients (OR 1.86, 95% CI 1.09 to 3.15). The second case-control study found no association. Neither study found a greater likelihood of current use of bisphosphonates among patients with atrial fibrillation. The reviewers concluded that bisphosphonates were associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents precluded any definitive conclusions with respect to risk.

Mortality

Only one review reported on mortality.(Lloyd-Jones and Wilkinson,2006)[124] The reviewers did not report an overall conclusion on this outcome, but reported from individual studies that: from one cohort study there was no difference between risedronate and placebo in all-cause mortality, cancer mortality, or mortality from cancer of the lung or gastrointestinal tract. A statistically non-significant reduction in deaths from cardiovascular causes in the risedronate group was largely due to a statistically significant reduction in stroke mortality in the combined risedronate groups (p=0.015); and from one prescription-event monitoring study that serious upper GI events included gastric, duodenal and peptic ulceration, gastritis, and duodenitis. However, only nine of the 502 reported deaths for which the cause of death was established were attributed to gastrointestinal causes.

Summary of reviews of adverse events

The fourteen reviews were published from 2001 to 2014. One review considered any antresorptive therapy,[132] ten considered any bisphosphonate therapy[120,122,126-131,133,134] and three

reported on adverse events associated with specific bisphosphonates (two in risedronate[121,123], one in alendronate or risedronate[124]) Four reviews included evidence from both observational studies and RCTs[120,124,126,134] and seven only included observational studies.[127-133] Five reviews reported on any adverse event, [120-123] whereas nine reported on specific adverse events (four in jaw osteonecrosis,[126-129] two in atypical fracture,[130,131] two in oesophogeal cancer,[132,133] one in atrial fibrillation[134]). Four reviews pooled data across studies in a meta-analysis. [129,131-133]

Evidence across these reviews indicates that alendronate, risedronate and oral ibandronate have similar rates of GI toxicity when compared with placebo. However, observational data suggests a high level of reporting of a number of conditions in the first month of therapy with alendronate or risedronate, particularly those affecting the upper gastrointestinal tract. Zoledronate may be compromised by renal toxicity and myalgias and arthralgias are evident in the acute phase following i.v. administration. Intravenous bisphosphonates, especially zoledronate, are more likely to predispose patients to osteonecrosis of the jaw, although absolute risk is very low. However, in addition to bisphosphonate use, there appear to be several other factors involved in the development of osteonecrosis of the jaw. There is an increased risk of atypical fracture among bisphosphonate users, however events are rare and long-term bisphosphonate therapy is not a prerequisite for development of atypical fractures. Moreover, the use of glucocorticoids and proton pump inhibitors are important risk factors. Bisphosphonates are associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents preclude any definitive conclusions with respect to risk. The review evidence for the use of bisphosphonates and oesophogeal cancer is equivoval.

e) Continuance and concordance

Alendronate

Two trials reported that at the end of treatment (36 months) that >80% participants were still taking study medication.(FIT I, Black *et al.*, 1998;[57] FIT II, Cummings *et al.*, 1998[66]) One trial reported that >60% of participants took 80% of their study medication.(Greenspan *et al.*, 2003[70])

Ibandronate

The ARIBON (Lester *et al.*, 2008[76]) trial reported that with more than 90% of participants took all of their monthly doses at 24 months. Mean duration on treatment was reported as 2.42 years in the placebo group and 2.48 years in the ibandronate 2.5 mg per day group in the BONE trial.(Chesnut *et al.*, 2004[45])

Risedronate

Boonen *et al.* (2009) reported that at 24 months 91% of placebo and 98% of risedronate 35 mg per week participants were compliant with the study drug. In the VERT-NA trial, Harris *et al.* (1999) [72] reported that 55% of placebo and 60% or risedronate 5 mg per month groups completed three years of medication. Taxel *et al.* (2010) reported that compliance with the study drug was 90% to 95% for all participants.

Zoledronate *vs.* alendronate

In the ROSE trial, Hadji *et al.* (2010)[108] reported that at 12 months 80.9% patients were compliant with alendronate therapy. Compliance with zoledronate was not reported.

Systematic review evidence for compliance and concordance

A supplementary search in Medline (Ovid) and Embase (Ovid) for systematic reviews reporting on compliance and continuance was undertaken on 6 January 2015. Keywords for 'compliance' were combined with the named drug intervention terms and a reviews search filter. The Medline search strategy is presented in Appendix 2. Fifty-seven additional citations were identified. These records were sifted by a single reviewer (MMSJ). Seven reviews were identified that summarised evidence for compliance and concordance across studies in bisphosphonates for osteoporosis. A summary of these reviews and their findings is presented in Appendix 4.

The review by Cramner *et al.* (2007)[135] included studies reporting one measure of compliance or persistence derived from administrative databases with patient demographic and prescription information. Compliance was measured as the medication possession ratio (MPR). Persistence was measured as the number of days of possession without a gap in refills, and the percentage of patients. Most of the therapies in the 14 included studies obtained were for oral daily or weekly bisphosphonates (alendronate and risedronate). Studies had observation periods of mainly 12 months. The reviewers reported that the mean MPR was consistently higher for weekly therapy (0.58 to 0.76) versus daily therapy (0.46 to 0.64). Patients receiving weekly bisphosphonates exhibited better persistence (length of persistence 194 to 269 days; 35.7% to 69.7% persistent) compared with those receiving daily therapy (length of persistence 134 to 208 days; 26.1% to 55.7% persistent). The reviewers concluded that although patients using weekly bisphosphonate medication follow their prescribed dosing regimens better than those using daily therapy, overall compliance and persistence rates were suboptimal

Imaz *et al.* (2010)[136] included observational studies that prospectively analysed administrative databases of pharmacy refills for measures of persistence and compliance in patients who were prescribed either bisphosphonates (mainly alendronate and risedronate) or other anti-osteoporosis medications. Follow-up periods needed to be one to 2.5 years. Compliance was to be measured by the medication possession ratio (MPR). Studies were pooled in meta-analyses. Fifteen studies were included in the review. The pooled persistence mean was 184.1 days (95% CI 163.9 to 204.3; five studies) and the pooled MPR mean was 66.9% (95% CI 63.3 to 70.5; five studies) at one year follow-up. Low compliance when compared with high compliance was significantly associated with increased overall fracture risk (RR 1.46, 95% CI 1.34 to 1.60; six studies) from one to 2.5 years after starting treatment. Compared to high compliance, low compliance was significantly associated with increased non-vertebral fracture risk (RR 1.16, 95% CI 1.07 to 1.26; three studies) from 1.9 to 2.2 years, increased hip fracture risk (RR 1.28, 95% CI 1.06 to 1.53; four studies) from 1.9 to 2.4 years and increased vertebral fracture risk (RR 1.43, 95% CI 1.26 to 1.63; two studies) from two to 2.2 years follow-up. The reviewers concluded that persistence and compliance were suboptimal for postmenopausal women who underwent bisphosphonate therapy for the treatment of osteoporosis.

Kothawala *et al.* (2007)[137] included 24 observational studies assessing pharmacological drug adherence in patients with osteoporosis. In the included studies bisphosphonates were the most frequently assessed drug; treatment duration ranged from one month to over 24 months; and a higher proportion of included patients were new users. However, the types of bisphosphonates were not reported. The outcomes of interest were grouped according to standardised definitions: persistence (how long a patient received therapy after initiating treatment); compliance (how correctly, in terms of dose and frequency, patients took their medication); and adherence (a combined measure of persistence and compliance). Outcome rates were pooled in a random-effects meta-analysis. Compliance data were extracted as the percentage of patients who reported following the dosing recommendations. Adherence data were extracted as the percentage of patients achieving a predefined medication possession ratio threshold. Across seven studies the pooled refill compliance rate was 68% at both seven to 12 months (95%CI 63 to 72) and at 13 to 24 months (95%CI 67 to 69). The pooled estimate from self-reported data (four studies) was 62% (95%CI 48 to 75) of patients following the recommended instructions within six months of starting treatment. Across six studies, the pooled estimate of patients achieving a MPR higher than 66% (one study) and higher than 80% (five studies) ranged from 53% (95%CI 52 to 54) for treatment lasting one to six months, to 43% (95%CI 32 to 54%) for treatment lasting 13 to 24 months. The authors

concluded that one third to one half of patients being treated with pharmacological drugs for osteoporosis did not take their medication as directed.

Lee *et al.* (2011)[138] reviewed 10 RCTs and observational studies. Compliance and persistence were evaluated but data were not pooled. Studies in osteoporosis medications including alendronate were evaluated. These reviewers reported that adherence at 12 months was higher with weekly over daily bisphosphonates (≥84% preference for weekly, medication possession ratios (MPR) 60 to 76% *vs.* 46 to 64%; persistence 43.6 to 69.7% *vs.* 31.7 to 55.7%). MPR reported for oral bisphosphonates were 68 to 71% at 12 months. At 2 years, only 43% of patients had MPR ≥80% for daily and weekly bisphosphonates. Observational studies (6 to12 months duration) reported discontinuation rates of 18 to 22% for daily and 7% for weekly bisphosphonates. Studies suggest patient preference for annual zoledronic acid infusions over weekly bisphosphonates (66.4 to 78.8% vs. 9.0 to 19.7%, respectively), but no data on compliance or persistence were available. The reviewers concluded that adherence is difficult to quantify and may not be exclusively influenced by the frequency of medication administration.

As part of a NICE report on adverse effects and persistence with oral bisphosphonates, Lloyd-Jones and Wilkinson (2006[124]) reported that across UK prescription-event monitoring studies that 24.5% of patients prescribed alendronate by general practitioners discontinued therapy within a year. The two most common reasons for stopping treatment were dyspeptic conditions (6.3%) and non-compliance (3.0%). These authors concluded that persistence may be improved by weekly rather than daily dosing regimens.

Mikyas *et al.*, 2014[139] reviewed treatment adherence in studies in male osteoporosis. Eighteen retrospective or prospective observational studies were included in the analysis. The reviewers reported that the definition and measure of medication adherence varied among studies, however that adherence was measured in terms of medication possession ratio (MPR) in most studies that reported adherence. Treatments were mainly bisphosphonates and mainly alendronate. Data were not pooled. Across studies, the percentage of males adherent to bisphosphonates [medication possession ratio (MPR)>0.8] over 12 months ranged from 32 % to 64 %. The reviewers concluded that one-third to two-thirds of men do not adhere to bisphosphonates.

Vieira *et al.* (2014)[140] reviewed 27 mainly observational studies of bisphosphonates (alendronate, ibandronate, risedronate and zoledronate) covering a wide range of outcomes regarding adherence and associated factors. No data were pooled and a narrative summary of

the included studies was reported. Amongst the included studies the reviewers summarised evidence from: one cohort study in which the proportion of days covered (described as equivalent of an MPR) was 82% with zoledronate i.v. and 58-62% with ibandronate i.v.; one cohort study in which overall compliance with oral alendronate, risedronate, or ibandronate was 43%; one cohort study in which persistence with therapy declined from 63% at 1 year to 46% at 2 years and 12% at 9 years amongst patients receiving alendronate and risedronate; one RCT in which the MPR was 93% to 100% amongst women taking weekly alendronate or monthly ibandronate; one retrospective observational study in women taking-weekly (alendronate or risedronate) or monthly ibandronate. Patients treated with a monthly regimen were 37% less likely to be non-persistent and were more compliant, with a 5% higher absolute MPR, than women treated with weekly regimens; and one cohort study in patients taking weekly risedronate or weekly alendronate in which patients initiated on weekly oral generic alendronate showed a statistically significant lower persistence to bisphosphonate therapy compared to patients initiated on weekly oral branded risedronate and weekly oral branded alendronate. Across all studies, the reviewers concluded that a monthly dosage is associated with better adherence compared to weekly dosage.

Summary of reviews of continuance and concordance

Seven reviews were identified published between 2006 and 2014. The majority of these reviews reported on aledronate and risedronate. Two reviews also included studies in ibandronate[140] and zoledronate.[138,140] The majority of reviews evaluated compliance as a medication possession ratio (MPR) and persistence measured as the number of days of possession. Data were pooled across studies by three reviews.[136-138]

Evidence across these reviews indicates that although patients using weekly bisphosphonate medication follow their prescribed dosing regimens better than those using daily therapy, overall compliance and persistence rates are suboptimal for postmenopausal women receiving bisphosphonate therapy for the treatment of osteoporosis. Furthermore, one third to one half of patients, including men being treated with bisphosphonates for osteoporosis did not take their medication as directed.

f) Health-related quality of life

Alendronate

A Quality of life assessment was reported by one RCT[67] using the Nottingham Health Profile.[141] Statistically significant improvements in all of the instrument's domains were reported with alendronate. Differences between treatments with placebo were not reported.

Ibandronate

Health-related quality of life was not reported by any trial evaluating ibandronate.

Risedronate

Health-related quality of life was not reported by any trial evaluating risedronate.

Zoledronate

In the HORIZON-RFT trial, quality of life outcomes were reported by Adachi *et al.* (2011)[105] Quality of life was assessed at 6, 12, 24 and 36 months using the EQ-5D Visual Analogue Scale (VAS) and utility scores (EuroQol instrument).[142] The authors report that at the end of the study, mean change from baseline in EQ-5D VAS was greater (higher score better) in the zoledronate treated group than the placebo group (7.67±0.56 *vs.* 5.42±0.56; p=0.0034). A statistically significant difference between treatments in EQ-5D VAS was also evident in: the subgroup of patients experiencing clinical vertebral fractures (8.86±4.91 *vs.* -1.69±3.42; p=0.0456), non-vertebral fractures (5.03±2.48 *vs.* -1.07±2.16; p=0.0393), and clinical fractures (5.19±2.25 *vs.* -0.72±1.82; p=0.0243) in favour of zoledronate. EQ-5D utility scores were comparable for zoledronate and placebo groups, but more participants in the placebo group consistently had extreme difficulty in mobility (1.74% *vs.* 2.13%; p=0.6238), self-care (4.92% *vs.* 6.69%; p=0.1013), and usual activities (10.28% *vs.* 12.91%; p=0.0775).

Zoledronate *vs.* alendronate

In the ROSE trial, Hadji *et al.* (2012)[71] assessed quality of life using the Qualeffo-41 questionnaire.[143] Hadji *et al.* (2010)[108] reported that in the alendronate group only the pain domain showed a significant improvement as compared to baseline. However, across all domains the differences between the treatments were not statistically significant.

g) Health resource use

Alendronate

The FIT I trial (Black *et al.*, 1996[57]) reported hospital admissions for fracture of 9.2% in the placebo group compared with 6.3% in the alendronate groups.

No other included RCT reported any hospitalisation and service use following fracture.

Systematic review evidence for health-related quality of life

A summary of reviews of health-related quality of life is presented in Section 6.1 of this assessment report.

Table 6: Outcome data reported by included RCTs

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
Alendronate vs. placebo				
Adami 1995[55] 24 months	*Numbers completing:* Of the original 286 patients (all doses), 17 were lost to follow-up and 9 withdrew consent during the study, n by group not reported *Reasons for withdrawal:* Thirteen patients discontinued treatment due to a clinical adverse experience (AE), and two due to a laboratory (not described) AE, n by group not reported	Not reported	Not an outcome	*Mean percent change (SD) from baseline:* PBO, -2.58 (7.28) ALN10mg, 1.19 (6.92) *Between-group difference:* p ≤ 0.01 *vs.* placebo *Numbers included in FN BMD analysis*: PBO, 67/71 (86%) ALN10mg/d, 62/68 (91%)
Black 1996[57] (FIT I) 36months	*Numbers with radiograph at follow-up:* PBO, 965/1005 (96.0%) ALN10mg/d, 981/1022 (96.0%) *Reasons for withdrawal:* Similar proportions of women in the two groups permanently discontinued study medication because of adverse experiences (96 [9·6%] PBO vs. 78 [7·6%]) ALN. Other reasons for withdrawal not reported	At closeout 87% of those assigned to PBO and 89% of those assigned to ALN were taking study medication and 96% in each treatment group had taken at least 75% of their pills since the last clinic visit	PBO: *New morphometric* vertebral fractures, 192/965 (19.9%) - 240 fractures; ≥*1 morphometric* vertebral fracture 145/965 (15%); ≥*2 morphometric* vertebral fractures 47/965 (4.9%); *Clinical vertebral* fractures 50/965 (1.3%); *Any clinical* fracture 183/1005 (18.2%); *Non-vertebral* 148/1005 (14.7%); *Hip* 22 (2.2%), *wrist* 41 (4.1%), *other* 99 (9.9%) ALN*: New morphometric* vertebral fractures: 83/981 (8.5%); ≥*1 new morphometric* vertebral fractures, 78/981 (8%) - 86 fractures; ≥*2 new morphometric* vertebral fractures, 5/981 (0.5%); *Clinical vertebral* fracture, 23/981 (0%);	*Mean percent change (SD) from baseline (extracted from graph):* PBO, -0.31 (5.7) ALN10mg/d, 3.54 (5.43) *Between-group difference:* 4·1% difference, p<0·001

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
			Non-vertebral 122/1022 (11.9%) *Hip* 11 (1.1%), *wrist* 22 (2.2%), *other* 100 (8%). *Between-group difference:* *New morphometric* vertebral fractures 47% lower (p<0·001) in ALN *≥1 new morphometric:* RR 0.53 (95%CI 0.41–0.68); *≥2 new morphometric* vertebral fractures, RR 0.10 (0.05–0.22); *Clinical vertebral* fracture, RH 0.45 (0.27–0.72); *Non-vertebral* RR 0.80 (0.63–1.01); *Hip* RR 0.49 (0.23–0.99); *wrist* RR 0.52 (0.31–0.87); *other* RR 0.99 (0.75–1.31)	
Cummings 1998[66] (FIT II) 36 months	*Numbers with radiograph at follow-up:* PBO, 2077/2218 (93.6%) ALN10mg/d, 2057/2214 (93.0%) *Reasons for withdrawal:* PBO, died 37 (16.6%), other 104 (4.7%) ALN10mg/d, died 35 (15.8%), other 122 (5.5%) *Stopped medication as rate of bone loss exceeded predetermined limits*: PBO, 22 (9.9%) ALN10mg/d, 12 (5.4%)	At closeout 82.5% of those assigned to PBO and 81.3% of those assigned to ALN were taking study medication and 96% in each treatment group had taken at least 75% of their pills since the last clinic visit	PBO: *≥1 vertebral* 78/2077 (3.8%); *≥2 vertebral* 10/2077 (0.2%); *Any clinical* 312/2218 (14.1%) *Non-vertebral* 294/2218 (13.3%) *Hip* 24 (1.1%); *wrist* 70 (3.2%) *Other clinical* 227/2218 (10.2%) ALN10mg/d: *≥1 vertebral* 43/2057 (2.1%); *≥2 vertebral* 4/2057 (0.2%); *Any clinical* 272/2214 (12.3%) *Non-vertebral* 261/2214 (11.8%) *Hip* 19/2214 (0.9%); *wrist* 83/2214 (3.7%); *Other clinical* 182/2214 (8.2%) *Between-group difference:* *≥1 vertebral* RH 0.56 (95%CI 0.73-1.01); p=0.002 *≥2 vertebral* RH 0.40 (0.13-12.4); p=0.11 *Any clinical* RH 0.86 (0.73-1.01); p=0.07	*Mean percent change (SD) from baseline (extracted from graph):* PBO, -0.8 (7.53) ALN10mg/d, 3.6 (7.53) *Between-group difference:* 4.6% difference, p<0·001

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
			Non-vertebral RH 0.88 (0.74-1.04); p=0.13 *Hip* RH 0.79 (0.43-1.44); p=0.44 *wrist* RH 1.19 (0.87-1.64); p=0.28; *Other clinical* RH 0.79 (0.65-0.96); p=0.02	
Bone 2000[59] 24 months	*Numbers completing*: PBO, 34/50 (68%) ALN10mg/d, 68/92 (73.9%) *Reasons for withdrawal:* PBO, AE 5 (10%); withdrew consent 7 (14%); lost to follow-up 4 (8%); protocol violation; 0 (0%) ALN10mg/d, AE 6 (6%); withdrew consent 10 (11%); lost to follow-up 5 (5.5%); protocol violation; 3 (3.3%)	Not reported	*Non-vertebral fractures (e.g., foot, ankle, rib) reported as AE:* PBO, 4/50 (8%) ALN10mg/d, 5/92 (5.4%) *Between-group difference:* Reported as not significant, p-value not reported	*Mean percent change (SD) from baseline:* PBO, -0.6 (6.78) ALN10mg/d, 2.9 (4.66) *Between-group difference:* ALN reported as significant *vs.* baseline and PBO, p-value not reported
Carfora 1998[62] 30 months	*Numbers completing*: not reported *Reasons for withdrawal:* Not reported	Not reported	*Vertebral fractures:* PBO, 4/34 (8.82%) ALN10mg/d, 1/34 (2.94%) *Between-group difference:* Not reported	Not reported
Chesnut 1995[63] 24 months	*Numbers completing*: Reports that of 188 enrolled (PBO; ALN10, 20 and 5mg) 164 (87%) completed 12 months, and 154 (82%) completed 24 months, n by group not reported *Reasons for withdrawal:* Reports that of the 34 withdrawals, 18 were due to AE, 1 to an adverse laboratory	Not reported	Not an outcome	*Mean percent change (SD) from baseline:* PBO, not reported ALN10mg/d, 5.03 (3.78) *Between-group difference:* P-value *vs.* PBO reported as <0.01

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	experience, 5 due to protocol deviations, and 10 due to voluntary withdrawal, n by group not reported			
Dursun 2001[67] 12 months	*Radiographic follow-up available for*: Ca 1000mg/d, 35/50 (70.0%) ALN10mg/d+Ca, 38/51 (74.5%) *Reasons for withdrawal:* Not reported	Not reported	*Vertebral fractures*: Ca 1000mg/d, 14/35 (40.0%) ALN10mg/d+Ca, 12/38 (31.6%) *Between-group difference:* Not reported	*Mean percent change (SD) from baseline:* Ca 1000mg/d, 2.33 (4.32) ALN10mg/d+Ca, 3.75 (6.16) *Between-group difference:* P<0.0001
Greenspan 2002[69] 24 months	*Numbers completing*: Not reported *Reasons for withdrawal:* Not reported	Not reported	*Clinical fractures (not described):* PBO, any 18/164 (11.0%); hip 4/164 (2.4%) ALN10mg/d, any 13/163 (8.0%); hip 2/163 (1.2%) *Between-group difference:* Reported as not significant, p-value not reported	*Mean percent change (SD) from baseline (extracted from graph):* PBO, -0.36 (0.82) ALN10mg/d, 2.84 (4.43) *Between-group difference:* 3.4% [CI, 2.3% to 4.4%]; p<0.001
Greenspan 2003[70] 36 months	*Numbers completing:* PBO, 83/93 (89.3%) ALN10mg/d, 85/93 (91.4%) *Reasons for withdrawal:* PBO, refused follow-up 8 (8.6%). Medical contraindication 1 (10.8%), death 1 (10.8%) ALN10mg/d, lost to follow-up 2 (2.2%), refused follow-up 4 (4.3%). Medical contraindication 1 (10.8%),	*Participants taking 80% of medication during study:* PBO, 63/93 (68%) ALN10mg/d, 58/93 (62%)	*Clinical fractures (not described):* PBO, 9/93 (10.0%) ALN10mg/d, 7/93 (8.0%) *Between-group difference:* Not reported	*Mean percent change (SD) from baseline (ALN extracted from graph):* PBO, -0.65 (5.11) ALN10mg/d, 4.2 (3.8) *Between-group difference:* Reported as significantly different, p-value not reported

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	death 1 (10.8%)			
Ho 2005[73] 12 months	*Numbers completing*: Ca 500mg/d, 26/29 (89.7%) ALN10+Ca, 28/29 (96.5%) *Reasons for withdrawal:* Ca 500mg/d, personal reasons 3 (10.3%) ALN10+Ca, personal reasons a (3.5%)	Not reported	Not an outcome	*Mean percent change from baseline:* Ca 500mg/d, -0.2 ALN10+Ca, 5.6 Variance estimates not reported *Between-group difference:* P<0.05
Klotz 2013[75] (CORAL) 12 months	*Numbers completing:* PBO, 92/102 (90%) ALN70mg/w, 78/84 (92.8%) *Reasons for withdrawal:* PBO, adverse event 6 (2%), withdrew consent 2 (2%), participant request 2 (2%) ALN70mg/w, withdrew consent 3 (3.6%), disease progression 1 (1.2%), lost to follow-up 1 (1.2%), non-compliance 1 (1.2%)	Reports that compliance (pill count) was similar (99% and 100%) between the two groups.	*Adverse event fracture (not described):* PBO, 3/102 (1.67%) ALN70mg/w, 1/84 (0.7%) *Between-group difference:* P=0.4395	*Mean percent change (SD) from baseline:* PBO, -2.06 (5.71) ALN70mg/w, 1.65 (7.53) *Between-group difference:* Not reported
Liberman 1995[78] 36 months	*Numbers completing*: PBO, 332/397 (83.6%) AL10mg/d, 170/196 (86.7%) *Reasons for withdrawal:* PBO, adverse events 24 (6%), other reasons (41, 10.3%) not reported AL10mg/d, adverse events 8 (4.1%), other reasons (18, 9.2%) not reported	Not reported	*Fractures:* PBO, *Vertebral* fractures 22/355 (6.2%); *non-vertebral* 38/397 (9.6%); *hip* 3/397 (0.8%); *wrist* 16/397 (4.0%) ALN5, 10, 20mg, *vertebral* fractures 17/526 (3.2%); *non-vertebral* 73/1012 (7.2%) *Between-group difference:* Vertebral fractures RR 0.52 (95%CI 0.28 to 0.95); p=0.03; non-vertebral RR 0.79 (95%CI 0.52 to	*Mean percent change (SD) from baseline (extracted from graph):* PBO, -1.28 (5.98) ALN10mg/d, 4.65 (6.58) *Between-group difference:* 5.9% (SE 0.5); p<0.001

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
			1.22); hip and wrist not reported Fractures by ALN dosage not reported *Between-group difference PBO vs. ALN10mg:* OR 0.45 (95%CI 0.18-1.13)	
Orwoll 2000[85] 24 months	*Numbers completing:* PBO, 79/95 (83%) ALN10mg/d, 125/146 (86%) *Reasons for withdrawal:* Not reported	Not reported	*Fractures:* PBO, new vertebral fractures vertebral 7/94 (7.1%); non-vertebral 5/94 (5.3%) ALN10mg/d, new vertebral fractures 1/146 (0.8%); non-vertebral 6/146 (4.1%) *Between-group difference:* New vertebral fractures p=0.02; non-vertebral p=0.8	*Mean percent change (SD) from baseline:* PBO, -0.1 (4.5) ALN10mg/d, 2.5 (4.52) *Between-group difference:* 2.6% (95%CI 1.6–3.7); p<0.001
Pols 1999[86] (FOSIT) 12 months	*Numbers completing*: PBO, 865/958 (90.0%) ALN10mg/d, 832/950 (88.0%) *Reasons for withdrawal:* Not reported	Not reported	*Non-vertebral fractures:* PBO, 37/958 (3.9%) ALN10mg/d, new 19/950 (2.0%) *Between-group difference:* 47% risk reduction (95%CI 10 to 70); p = 0.021	*Mean percent change (SD) from baseline:* PBO, -2.0 (4.5) ALN10mg/d, 2.3 (4.5) *Between-group difference:* 2.4% (95%CI 2.0 to 2.8); p<0.001
Saag 1998[93] 48 weeks Adachi 2001 [100] 24 months	*Numbers BMD data reported for 12mo:* PBO, 142/159 (89.3%) ALN10mg/d, 145/157 (92.4%) *Numbers fracture data reported for 12months:* PBO, 134/159 (84.2%) ALN 5/10mg, 266/318 (83.6%) *24 months:* not reported	Not reported	*Number (%) of fractures 12 months:* PBO, vertebral 5/134 (3.7%); Men 1/48 (2.1%); Postmenopausal women 4/53 (7.6%); Non-vertebral 7/159 (4.4%): ALN5/10mg/d, vertebral 6/266 (2.3%); Men 1/74 (1.4%); Postmenopausal women 5/134 (3.7%); Non-vertebral 14/318 4.4%) *Between-group difference 48 weeks:*	*12 months - Mean percent change (SD) from baseline:* PBO, -1.2 (4.77) ALN10mg, 1.0 (4.82) *24 months:* PBO, -2.93 (6.26), n=53 ALN10mg/d, 0.61% (4.71), n=51 *Between-group difference:*

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	Reasons for withdrawal 12 months: PBO, adverse events 8 (5%), other withdrawals not reported AL10mg/d, adverse events 6 (4%), other withdrawals not reported *24 months:* not reported		Vertebral fractures all RR 0.6 (95%CI 0.1-4.4) *24 months – fractures:* PBO, Vertebral fractures 4/59 (6.8%); of which women 4/40 (10.0%), men 0/19 (0%); non-vertebral 6/61 (9.8%) ALN5/10mg/d, Vertebral fractures 1/143 (0.7%); of which women 1/97 (1.0%), and men 0/46 (0%); non-vertebral 8/147 (5.4%) *Between-group difference 24 months:* p=0.026 Fractures by ALN dosage not reported	p≤0.001
Shilbayeh 2004[95] 12 month	*Numbers completing*: PBO, 18/36 (50%) ALN10mg/d, 20/27 (74%) *Reasons for withdrawal:* All women (osteoporotic and osteopenic), n=118: adverse event 9 (7.6%), personal reason 21 (17.8%), lost to follow-up 17 (14.4%), non-compliance 6 (5%), other 3 (2.5%)	Not reported	Not an outcome	*Mean percent change from baseline (SD extracted from graph):* ALN10mg, 0.79 (7.82) vs. young adult PBO, 0.00 (6.36) vs. young adult ALN10mg, 1.84 (13.59) vs. age-matched PBO, 1.71 (13.87) vs. age-matched Comparative values for young adult and age-matched not reported *Between-group difference:* not reported, p<0.01 compared with baseline reported for ALN group
Smith 2004[96]	*Numbers completing:*	Not reported	Not an outcome	*Change in T score:*

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
12 months	PBO, 55/79 (70%) ALN10mg/d, 41/65 (36%) *Reasons for withdrawal:* Report that of those who withdrew, main reasons included: voluntary withdrawal (38%); adverse event (36%); loss to follow up (16%); and protocol violation (10%), n by group not reported			PBO ITT, -0.0031 (0.24) PBO PP, 0.0294 (0.29) ALN10mg ITT, 0.0565 (0.25) ALN10mg PP, 0.0644 (0.19) *Change in Z score:* PBO ITT, 0.0587 (0.24) PBO PP, 0.1021 (0.23) ALN10mg ITT, 0.1328 (0.23) ALN10mg PP, 0.1498 (0.24) *Between-group difference:* T score ITT, p=0.816; T score PP, p=0.811; Z score ITT, p=0.091; Z score PP, p=0.334
Ibandronate vs. placebo				
Chesnut 2004[45]; Chesnut 2005[46] (BONE) 36 months	*Numbers completing treatment*: PBO, 628/982 (64%) IBN2.5mg/d, 648/982 (66%) IBN 20mg eod, 12 doses/m, 662/982 (67.4%) *Reasons for withdrawal:* PBO, did not receive medication 7 (1%), AE 180 (18.3%), other 167 (17%) IBN2.5mg/d, did not receive medication 5 (<1%), AE 175 (17.8%), 154 other (15.6%) IBN 20mg eod, 12 doses/m, did not receive medication 5 (<1%), AE 178 (18.1%), other	*Mean duration on treatment yrs.:* PBO, 2.42 IBN2.5mg/d, 2.48 IBN 20mg eod, 12 doses/m, 2.46	*New vertebral*: PBO, 93/975 (9.56%) IBN2.5mg/d, 46/977 (4.7%) IBN 20mg, 48/977 (4.9%) *Between-group difference vs. PBO:* IBN2.5mg/d, RR 62 (95%CI 41-74); p=0.0001 IBN 20mg, RR 50 (95%CI 26-66); p=0.0006 *New or worsening vertebral:* PBO, 2.42, 101/975 (10.4%) IBN2.5mg/d, 50/977 (5.1%) IBN 20mg, 57/977 (5.8%) *Clinical vertebral*: PBO, 2.42, 52/975 (5.3%) IBN2.5mg/d, 27/977 (2.8%)	Not an outcome

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	137 (14%)		IBN 20mg, 27/977 (2.8%) *Between-group difference vs. PBO:* IBN2.5mg/d, p=0.00117 IBN 20mg; p=0.0143 *Clinical OP*: PBO, 2.42, 127/975 (13%) IBN2.5mg/d, 113/977 (11.6%) IBN 20mg, 109/977 (11.2%) *Between-group difference vs. PBO:* not reported *Clinical non-vertebral*: PBO, 2.42, 80/975 (8.2%) IBN2.5mg/d, 89/977 (9.1%) IBN 20mg, 87/977 (8.9%) *Between-group difference vs. PBO:* not reported	
Lester 2008[76] (ARIBON) 24 months	*Numbers completing:* PBO, 19/25 (76%) IBN150mg/m, 21/25 (84%) *Reasons for withdrawal:* PBO, reduced BMD at yr. 1, 2 (8%); recurrent disease, 2 (8%0, bowel carcinoma, 1 (4%), CVA (not described), 1 (4%) IBN150mg/m, Vaginitis, 1 (4%); joint pain, 1 (4%)	Reports that tablet compliance of the ibandronate was very good with more than 90% of study patients taking all of their monthly doses	Reports that no fragility fractures were reported. Three patients taking placebo (wrist = 1, shoulder = 1, rib = 1) experienced a traumatic fracture. Two patients taking ibandronate (wrist = 1, hip = 1) experienced a traumatic fracture. *Between-group difference:* Not reported	Not an outcome
McClung 2009[82] 12 months	*Numbers completing*: PBO, 73/83 (88%) IBN150mg/m, 65/77 (84%) *Reasons for withdrawal:*	Not reported	*Fracture adverse event:* PBO, 2/83 (2%) - both fractures of the foot associated with traumatic events IBN150mg/m, 2/77 (3%) - one subject had a fracture of the radius while another subject	*Mean percent change from baseline (SD):* PBO, -0.73 (4.16) IBN150mg/m, 1.09 (2.87)

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	Not reported		had both a rib fracture and an upper limb fracture associated with traumatic events. *Between-group difference:* Not reported	*Between-group difference:* Not reported
Ibandronate dose ranging trials				
Delmas 2006[49] (DIVA) 12 months Eisman 2008[50] 24 months	*Numbers completing 12 months*: IBN2.5mg/d, 409/470 (87%) IBN2mg/iv, 2/m, 382/454 (84%) IBN3mg/iv, 3/m, 394/471 (84%) *24 months*: 384/470 (83%); 361/454 81%); 372/471 (79%) *Reasons for withdrawal 24 months*: IBN2.5mg/d, AE 46 (9.8%), death 3 (<1%), no follow-up 2 (<1%), refused treatment 28 (6%), other 2 (<2%) IBN2mg/iv, AE 41 (9%), death 3 <1%), no follow-up 6 (1.3%), refused treatment 30 (6.6%), other 7 (1.5%) IBN3mg/iv, AE 53 (11.2%), death 2 (<1%), no follow-up 6 (1.9%), refused treatment 35 (7.4%), other 1 (<1%)	*12 months*: Reports poor compliance with the oral [n=248] or IV [n=165], n by group not reported *24 months*: noncompliance with the daily regimen (~18%), noncompliance with the IV regimens (~12%)	*12 months*: Reports that in total, 43 patients (3.1%) experienced clinical fractures (radiographically confirmed), including Non-vertebral fractures: 13 fractures each occurred in the every-2-months group and the every-3-months group, and 17 fractures occurred in the oral-treatment group. 43 equals 3.1% inconsistent with safety n reported. *24 months clinical osteoporotic fractures (including fractures of the vertebrae, clavicle, scapula, ribs, pelvis, sternum, humerus, forearm, femur, patella, tibia, fibula, ankle, and carpus)* IBN2.5mg/d, 29/465 (6.2%) IBN2mg/iv, 2/m, 21/448 (4.7%) IBN3mgiv, 3/m, 23/469 (4.9%) *Between-group difference:* Not reported	*Mean percent change from baseline (SD) extracted from graph 12 months*: IBN2.5mg/d, 1.6 (4.18) IBN2mg/iv, 2.0 (3.89) IBN3mg/iv, 2.3 (3.87) *Between-group difference:* Not reported *24 months*: IBN2.5mg/d, 2.01 (5.65) IBN2mg/iv, 2.62 (4.21) IBN3mg/iv, 2.32 (4.70) *Between-group difference:* Not reported
Miller 2005[47] Reginster 2006[48] (MOBILE) 12 and 24 months	*Numbers completing 12 months*: IBN2.5mg, 335/402 (83%) IBN50/50mg, 347/402	Reports the measures of compliance do not allow conclusions on differences in therapeutic adherence.	Reports clinical fractures identified as adverse events showed no statistically significant differences between the treatment arms after 1 year	*Mean percent change (SD) from baseline (extracted from graph) 12 months:* IBN2.5mg, 1.71 (3.68)

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	(86.3%) IBN100mg/m, 340/404 (84.2%) IBN150mg/m, 344/401 (84.1%): *24 months*: 325 (80.8%); 328 (81.6%); 316 (78%); 322 (80.3%) *Reasons for withdrawal 24 months*: IBN2.5mg, death 41 (10%), no follow-up 3 (<1%), refused treatment 20 (5%), other 6 (1.5%) IBN50/50mg, death 32 (8%), no follow-up 2 (<1%), refused treatment 29 (7%), other 5 (1.2%) IBN100mg, death 44 (11%), no follow-up 4 (1%), refused treatment 29 (6.4%), other 3 (<1%) IBN150mg, death 37 (9.2%), no follow-up 5 (1.2%), refused treatment 32 (7.9%), other 0	Data not presented	*Clinical osteoporotic fractures recorded as adverse events at 24 months:* IBN2.5mg, 24 (6.1%) IBN50/50mg, 29 (7.3%) IBN100mg/m, 24 (6.1%) IBN150mg/m, 27 (6.8%): *Between-group difference:* not reported	IBN50/50mg, 1.84 (3.68) IBN100mg/m, 1.92 (3.64) IBN150mg/m, 2.22 (3.83) *Between-group difference:* not reported *24 months:* IBN2.5mg, 1.91 (4.45) IBN50/50mg, 2.08 (4.09) IBN100mg/m, 2.65 (3.74) IBN150mg/m, 3.12 (7.03) *Between-group difference:* not reported
Risedronate vs. placebo				
Boonen 2009[60] 24 months	*Numbers completing:* PBO, 75/93 (80.6%) RIS35mg/w, 175/191 (91.6%) *Reasons for withdrawal:* PBO, Adverse event, 9 (9.7%); Protocol violation, 1 (1.1%); Voluntary withdrawal, 7 (7.5);	*Compliant with study drug:* PBO, 91% RIS35mg/w, 98%	*Fractures:* PBO, *New vertebral* fractures, 0 *Clinical fractures*, 6/93 (6%) RIS35mg/w, *New vertebral fractures*, 1/191 (5.2%) *Clinical fractures*, 9/191 (5%) *Between-group difference:*	*Mean percent change from baseline (SD) extracted from graph:* PBO, 0.73 (3.28) RIS35mg/w, 1.71 (3.46) *Between-group difference:* Reports significantly greater

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	lost to follow-up, 1 (1.1%) RIS35mg/w, Adverse event, 7 (4%); Voluntary withdrawal, 9 (5.1%)		Reported as no differences in fracture rates between groups	increases in femoral neck BMD were observed at month 24 and endpoint in the risedronate group compared with placebo
Choo 2011[64] 24 months	*Numbers included in analysis:* PBO, 52/52 (100%) RIS35mg/w, 52/52 (100%) *Reasons for withdrawal:* not reported	Not reported	Not an outcome	*percentage change from baseline (SD:* PBO, -5.56 (21.06) RIS35mg/w, -2.55 (20.84) *Between-group difference:* p = 0.4670, unclear if from baseline or *vs.* PBO
Cohen 1999[65] 12 months	*Numbers completing men and women:* PBO, 57/77 (74.0%) RIS5mg/d, 62/76 (81.6%) *Reasons for withdrawal men and women:* Across all groups (Inc. RIS2.5mg) 12 withdrew as a result of adverse events, 21 could not comply with the study protocol, 15 withdrew voluntarily, and 3 were lost to follow-up.	Not reported	*Vertebral fracture*: PBO, premenopausal women 0/11 (0.0%); postmenopausal women 5/24 (20.8%) RIS5mg/d, premenopausal women 0/10 (0.0%); postmenopausal women 2/24 (8.3%) *Between-group difference:* Men and women P=0.072	*Mean percent change from baseline (SD)* *Premenopausal women:* PBO, -1.2 (4.64) RIS5mg/d, -3.3 (4.74) *Postmenopausal:* PBO, -0.9 (5.75) RIS5mg/d, -2.8 (5.1) *Between-group difference:* Women only, not significant Men and women P < 0.001
Fogelman 2000[68] (BMD-MN) 24 months	*Numbers completing*: PBO, 143/180 (79.4%) RIS5mg/d, 139/177 (78.5%) *Reasons for withdrawal:* PBO, AE 14 (8%), other reasons not reported RIS5mg/d, AE 19 (11%), other	Not reported	*Fractures recorded as AEs:* PBO, *Vertebral fractures* 17/125 (14.0%); *non-vertebral* 13/125 (9.0%) RIS5mg/d, *Vertebral fractures* 8/112 (7.0%); *non-vertebral* 7/112 (5.0%) *Between-group difference:* Not reported	*Mean percent change from baseline (SD):* PBO, -1.0 (0.32) RIS5mg/d, 1.3% (0.44) *Between-group difference:* P<0.001

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	reasons not reported			
Hooper 2005[74] 24 months	*Numbers completing*: PBO, 93/125 (74.4%) RIS5mg/d, 103/129 (79.8%) *Reasons for withdrawal:* PBO, voluntary 16 (12.8%), AE 8 (6.4%), protocol violation 5 (4%), lost to follow-up 1 (<1%), other 2 (1.6%) RIS5mg/d, voluntary 12 (9.6%), AE 7 (5.6%), protocol violation 5 (3.9%), other 2 (1.5%)	Not reported	*Fractures:* PBO, *new vertebral* fractures 10/125 (8.3%); *non-vertebral* 6/125 (4.8%) RIS5mg/d, *new vertebral* fractures 10/129 (7.7%); *non-vertebral* 5/129 (3.9%) *Between-group difference:* Reported as not significant, p-value not reported	*Mean percent change (SD) from baseline (extracted from graph):* PBO, -2.43 (3.69) RIS5mg/d, 2.29 (2.24) *Between-group difference:* 3.30%; p≤0.05
Harris 1999[72] 36 months (VERT-NA) Ste-Marie 2004[101] 60 months	*Numbers completing 36 months*: PBO, 450/815 (55.2%) RIS5mg/d, 489/813 (60.1%) *60 months*: 33/42 (78.6%) and 41/44 (93.2%) *Reasons for withdrawal 36mo:* PBO, AE 136 (16.6%), voluntarily withdrew144 (17.7%), protocol violation 39 (4.8%), lost to follow-up 21 (2.6%), treatment failure 8 (1%), other 17 (2.9%) RIS5mg/d, AE 138 (17%), voluntarily withdrew119 (14.6%), protocol violation 32 (3.9%), lost to follow-up 14 (17.2%), treatment failure 3 (<1%), other 18 (2.2%)	55% in the placebo, 60% in the RIS5mg/d group completed 3 years of medication.	*Fractures 36 months*: PBO, *Vertebral* 93/678 (16.3%); *non-vertebral* fractures 52/815 (8.4%); *hip* 15/815 (1.8%); *wrist* 22/815 (2.7%); *humerus* 10/815 (1.2%) RIS5mg/d, *Vertebral* 61/696 (11.3%); *non-vertebral* fractures 33/812 (5.2%); *hip* 12/812 (1.0%); *wrist* 14/812 (1.7%); *humerus* 4/812 (0.5%) *Between-group difference:* Vertebral 41% (95%CI 18-58%); p=0.003 Non-vertebral 39% (95%CI 6-61%);p=0.02 *Fractures 60 months*: PBO, *Vertebral* (7.1%); *non-vertebral* fractures (16.7%) RIS5mg/d, *Vertebral* (9.1%); *non-vertebral* fractures (4.5%) *Between-group difference:*	*Percent change from baseline (SD from graph) 36 months:* PBO, -1.2 (9.21) RIS5mg/d, 1.6 (12.83) *Between-group difference:* P<0.05 *Between-group difference 60 months reported as:* 4.7% - no variance estimate or p-value reported

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	60 months: PBO, 3, voluntary 4 RIS, voluntary 4		Not reported	
Reginster 2000[87] (VERT-MN) 36 months Sorensen 2003 [102] 60 months	*Numbers completing*: PBO, 221/407 (54.3%) RIS5mg/d, 251/407 (61.7%) *60 months*: 105/130 (80.8%) and 115/135 (85.2%) *Reasons for withdrawal:* PBO, AE 83 (19.7%), voluntary 58 (14.2%), other 45 (11%) RIS5mg/d, AE 65 (16%), voluntary 56 (13.8%), other 35 (8.6%) *60 months:* PBO, AE 16, protocol violation 2, voluntary 3, other 4 RIS5mg/d, AE 10, protocol violation 1, voluntary 6, other 3	Not reported	PBO, PBO, *new vertebral* fractures 89/346 (29.0%); *non-vertebral* 51/406 (16.0%); *hip* 11/406 (4.7%); *wrist* 21/406 (5.2%); *humerus* 14/406 (3.4%) RIS5mg/d, *new vertebral* fractures 53/344 (18.1%); *non-vertebral* 36/406 (10.9%); *hip* 9/406 (3.4%); *wrist* 15/406 (3.7%); *humerus* 7/406 (1.7%) *Between-group difference:* *new vertebral* RR 0.51 (95%CI 0.36-0.73); p<0.001 *non-vertebral* RR 0.67 (95%CI 0.44-1.04); p=0.063 *60 months*: PBO, *Vertebral* 29/103 (28.2%); *non-vertebral* 11/130 (8.5%); *humerus* 6/130 (4.6%) RIS5mg/d, *Vertebral* 15/109 (13.8%); *non-vertebral* 7/135 (5.2%); *humerus* 3/135 (2.2%) *Between-group difference:* Vertebral 59% (95%CI 0.19-0.79); p=0.01	*Mean percent change (SD) from baseline (extracted from graph):* PBO, -0.97 (7.46) RIS5mg/d, 2.09 (7.67) *Between-group difference:* 3.1% (95% CI: 1.8, 4.5); p<0.001 *60 months (SD from graph)*: PBO, -2.3 (6.84) RIS5mg/d, 2.2 (10.46) *Between-group difference:* p<0.05
Leung 2005[77] 12 months	*Numbers completing*: Not reported. *Reasons for withdrawal:* Overall, 5 migration, 1 stroke, 2 GI upset; n by group not	Not reported	*Fractures:* Reports that there were no symptomatic fractures in both groups during the study.	*Mean percent change from baseline (SD estimated from graph):* PBO, 1.1 (5.25) RIS5mg/d, 1.8 (3.9)

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	reported			*Between-group difference:* p<0.0001
McClung 2001[80] 12 months	*Numbers completing*: PBO, 1584/3134 (50.5%) RIS2.5+5mg groups, 4000/6197 (64.5%) *Reasons for withdrawal:* not reported		*Hip fracture all women:* PBO, 95/3134 (3.9%) RIS2.5+5mg groups, 317/6197 (2.8%) *Between-group difference:* RR 0.7 (95%CI 0.6-0.9); p=0.02 *Hip fracture age 70-79:* PBO, 46/1821 (3.2%) RIS2.5+5mg groups, 55/3624 (1.9%) *Between-group difference:* RR 0.6 (95%CI 0.4-0.9); p=0.009 *Hip fracture age 70-79:* PBO *vs.* RIS5mg/d *Between-group difference:* RR 0.7 (95%CI 0.4-1.1) *Hip fracture age 80+:* PBO, 82/2573 (4.2%) RIS2.5+5mg groups, 49/1313 (5.1%) *Between-group difference:* RR 0.8 (95%CI 0.6-1.2); p=0.35 *Non-vertebral all women:* PBO, 351/3134 (11.2%) RIS2.5+5mg groups, 317/6197 (9.4%) *Between-group difference:* RR 0.8 (95%CI 0.7-1.0); p=0.03 Fractures by ALN dosage for all women or women 80+ years not reported	*Between-group difference in women age 70-79:* PBO vs. RIS5mg/d, 3.4% Data by group and p-value not reported
Reid 2000[88] 12 months	*Numbers completing:* PBO, 70/96 (74.0%)	Not reported	*New vertebral fractures men and women:* PBO, 35/60 (37%)	*Mean percent change (SD) premenopausal women:*

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	RIS5mg/d, 81/100 (81.0%) *Reasons for withdrawal:* AEs 12%, voluntary 7%, lost to follow-up/protocol violation 3%; n by group not reported		RIS5mg/d, 34/60 (35%) *Between-group difference:* Not reported	PBO, 1.3 (4.92) RIS5mg/d, 0.7 (3.39) *Postmenopausal women:* PBO, -0.5 (3.08) RIS5mg/d, 1.8 (4.64) *Between-group difference:* Not reported. P<0.05 for RIS5mg in postmenopausal women *vs.* baseline
Ringe 2006[91] 12 months Ringe 2009[103] 24 months	*Numbers completing:* reports that all 316 patients were re-examined at month 12 *Numbers completing 24 months:* PBO, 152/158 (96%) RIS5mg/d, 148/158 (93.5%) *Reasons for withdrawal:* All due to personal reasons	Not reported	*New vertebral fracture 12 months:* PBO, 20/158 (12.7%) RIS5mg/d, 3/60 (5.0%) *Between-group difference:* P=0.028 *24 months:* PBO, 33/148 (22.3%) RIS5mg/d, 18/152 (11.8%) *Between-group difference:* P=0.032	*Mean percent change 12 months:* PBO, 0.2% RIS5mg/d, 1.8% *Between-group difference:* P<0.0001 *24 months:* PBO, 0.6% RIS5mg/d, 3.2% *Between-group difference:* P<0.0001 Variance estimates not reported
Taxel 2010[97] 6 months	*Numbers included in analysis:* PBO, 20/20 (100%) RIS35mg/w, 20/20 (100%)	Reports compliance with the study drug was 90–95% for all patients	Not an outcome	*Mean percent change (SD) from baseline:* PBO, -2.0 (2.72) RIS35mg/w, 0.0 (2.72) *Between-group difference:* P<0.01

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
Zoledronate vs. placebo				
Black 2007[58] (HORIZON-PFT) 36 months	*Numbers completing:* PBO, 3248/3889 (83.5%) ZOL5mg/y, 3269/3876 (84.3%) *Reasons for withdrawal:* Reports the primary reasons that patients in both study groups did not complete follow-up were adverse events, withdrawal of consent, loss to follow-up, and death. Numbers not reported	A total of 6260 patients (81%) received all three infusions.	*Fractures:* PBO, *Morphometric vertebral* fracture (stratum 1 – no OP meds [N=3039] proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture n=2853), 310/2853 (10.9%) *Hip* fracture, 88/3861 (2.3%) *Non-vertebral* fracture, 388/3861 (10.0%) *Any clinical* fracture, 456/3861 (11.8%) *Clinical vertebral* fracture, 84/3861 (2.2%) *Multiple (≥2%) morphometric vertebral* fractures (stratum 1 – no OP meds 3039 proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture n=2853), 66/2853 (2.3%) ZOL5mg/y, *Morphometric vertebral* fracture (stratum 1 – no OP meds [N=3045] proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture n=2822), 92/2822 (3.3%) *Hip* fracture, 52/3875 (1.3%) *Non-vertebral* fracture, 292/3875 (1.3%) *Any clinical* fracture, 308/3875 (8.0%) *Clinical vertebral* fracture, 19/3875 (0.5%) *Multiple (≥2%) morphometric vertebral* fractures (stratum 1 – no OP meds 3045 proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture n=2822), 7/2822 (0.2%)	*Mean percent change (SD) from baseline (PBO extracted from graph):* PBO, -0.04 (8.88) ZOL5mg/y, 5.06 (8.48) *Between-group difference:* 5.06% (95%CI 4.76-5.36); p<0.001

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
			Between-group difference: *Morphometric vertebral [Stratum I]* RR 0.30 (95%CI 0.24-0.38) *Hip* HR 0.59 (95%CI 0.42-0.83) *Non-vertebral* fractures, *all clinical* fractures, and *clinical vertebral* fractures p<0.001	
Lyles 2007[79] (HORIZON-RFT) 36 months	*Numbers completing:* PBO, 746/1062 (70%) ZOL5mg/y, 770/1065 (72.3%) *Reasons for withdrawal:* PBO, Died, 142 (13.4%); Withdrew consent, 108 (10.2%); lost to follow-up, 28 (2.6%); adverse events, 18 (1.7%); administrative problem, 8 (1.3%); protocol violation, 7(<1%); abnormal lab vale, 3 (<1%); unsatisfactory therapeutic effect, 1 (<1%) ZOL5mg/y, Died, 102 (9.5%); Withdrew consent, 120 (11.2%); lost to follow-up, 35 (3.3%); adverse events, 21 (1.9%); administrative problem, 9 (1%); protocol violation, 4 (<1%); abnormal lab value, 4 (<1%)	Not reported	*Fractures*: PBO, *Any new clinical*, 139/1062 (13.1%) *Non-vertebral*, 107/1062 (10.1%) *Hip*, 33/1062 (3.1%) *Vertebral*, 39/1062 (3.7%) ZOL5mg/y, *Any*, 92/1065 (8.6%) *Non-vertebral*, 79/1065 (7.1%) *Hip*, 23/1065 (2.2%) *Vertebral,* 21/1065 (2.0%) *Between-group difference:* *Any new clinical*, HR 0.65 (95%CI 0.50–0.84); p=0.001 *Non-vertebral*, 0.73 (0.55–0.98); 0.03 *Hip*, 0.70 (0.41–1.19); 0.18 *Vertebral*, 0.72 (0.56–0.93); 0.01	*Mean percent change from baseline* PBO, -0.7 ZOL5mg/y, 3.6 *Between-group difference:* p<0.001
Boonen 2012[61] 24 months	*Numbers completing:* PBO, 540/611 (88.4%) ZOL5mg/y, 530/588 (90.1%) *Reasons for withdrawal:* PBO,	Not reported	*One or more new morphometric vertebral fractures*: PBO, 28/574 (4.9%) ZOL5mg/y, 9/553 (1.6%)	*Mean percent change from baseline (SD estimated from graph):* PBO, 0.1 (4.6); n=63 ZOL5mg/y, 3.4 (4.49); n=56

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	22 (3.6%) Withdrew consent; 18 (2.9%) Died; 11 (1.8%) Had adverse event; 12 (2.0%) Were lost to follow-up; 4 (0.7%) Had protocol deviation; 4 (0.7%) Had unsatisfactory therapeutic effects ZOL5mg/y, 25 (4.3%) Withdrew consent; 15 (2.6%) Died; 11 (1.9%) Had adverse event; 4 (0.7%) Were lost to follow-up; 3 (0.5%) Had protocol deviation 35 (6.0%) Did not have baseline assessment and at least one assessment of the primary efficacy variable after baseline		*Between-group difference:* RR 0.33 (95%CI 0.16-07.70); p=0.002	*Between-group difference:* P<0.05
McClung 2009[81] 24 months	*Numbers completing*: PBO, 188/202 (93.1%) ZOL5mg/y, 154/181 (85.1%) *Reasons for withdrawal:* PBO, abnormal test result, 1 (<1%); AE, 1 (<1%); lost to follow-up, 2 (1.1%), protocol violation, 1 (<1%); withdrew consent, 9 (4.8%) ZOL5mg/y, AE, 3 (1.9%); lost to follow-up, 6 (6.2%), protocol violation, 2 (1.3%); withdrew consent, 16 (10.4%)	Not reported	Not an outcome	*Mean percent change from baseline (SD):* PBO, -1.35 (4.09) ZOL5mg/y, 1.64 (4.14) *Between-group difference:* P<0.001
Head-to-head – Alendronate vs. Ibandronate				
Miller 2008[83] (MOTION)	*Numbers completing*: ALN70mg/w, 785/873 (90%)	Not reported	*Osteoporotic fractures recorded as AEs*: ALN70mg/w, 17/859 (2.0)	*Mean percent change from baseline (SD):*

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
12 months	IBN150mg/m, 863/874 (89%) *Reasons for withdrawal:* Not reported		*Vertebral:* 5/859 (<1) *Non-vertebral:* 12/859 (1.4) IBN150mg/m, 18/874 (2.1) *Vertebral:* 5/874 (<1) *Non-vertebral:* 14/874 (1.6) *Between-group difference:* Not reported	ALN70mg/w, 2.1 (1.77) IBN150mg/m, 2.3 (2.12) *Between-group difference:* Reports that gains in FN BMD were similar with both treatments. P-value not reported
Atmaca 2006[56] 12 months	*Outcomes reported for*: RIS5mg/d, 14/14 (100%) ALN10mg/d, 16/16 (100%)	Not reported	Not an outcome	*End of study value (SD) [% change]:* RIS5mg, 0.612 (0.06) [1.5%] ALN10mg, 0.609 (0.06) [1.5%] Variance estimates not reported for % change *Between-group difference:* P<0.001
Muscoso 2004[84] 24 months	*Outcomes reported for*: RIS5mg/d, 100/100 (100%) ALN10mg/d, 1000/1000 (100%)	Not reported	*Fractures:* RIS5mg/d, 4 (2 Vertebral, 1 Femoral, 1 wrist) ALN10mg/d, 0 Not reported if unit of analysis is patient or fracture. *Between-group difference:* Not reported	Not an outcome
Sarioglu 2006[94] 12 months	*Outcomes reported for*: RIS5mg/d, 25/25(100%) ALN10mg/d, 25/25 (100%)	Not reported	*Fractures:* Reports that no fractures were detected throughout the study	*Mean percent change from baseline (SD):* RIS5mg/d, 3.7 (4.82) ALN10mg/d, 2.6 (3.02) *Between-group difference:* Reported as not significant, p-value not given

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
Rosen 2005[92] (FACT) 12 months Bonnick 2005[106] 24 months	*Numbers completing 12 months*: ALN70mg/w, 438/520 (84.2%) RIS35mg/w, 454/533 (85.2%) *24 months*: 375/411 (91.2%) and 375/414 (90.6%) *Reasons for withdrawal 12 months:* ALN70mg/w, AE 33 (6.3%), withdrew consent 29 (5.6%), lost to follow-up 14 (2.7%), moved 4 (0.8%), protocol deviation 2 (0.4%) RIS35mg/w, AE 33 (6.2%), withdrew consent 28 (5.3%), lost to follow-up 9 (1.7%), moved 3 (0.6%), protocol deviation 5 (0.9%), Lab AE 1 (0.2%) *24 months*: Not reported	Not reported	*Fractures recorded as adverse events at 12 months:* ALN70mg/w, 26/520 (5.0%) RIS35mg/w, 20/533 (3.8%) *Between-group difference:* Not reported *24 months:* ALN70mg/w, 34/411 (8.3%) RIS35mg/w, 34/414 (8.2%) *Between-group difference:* Not reported	*Mean percent change (SD) from baseline (extracted from graph) 12 months:* ALN70mg/w, 1.6 (5.39) RIS35mg/w, 0.9 (4.39) *Between-group difference:* 0.7% (95%CI 0.1-1.2); p<0.005 *24 months:* ALN70mg/w, 2.8 (4.45) RIS35mg/w, 1.0 (5.23) *Between-group difference:* 0.8% (95%CI 0.3–1.4%); p<0.005
Reid 2006[89] (FACTS) 12 months Reid 2008[107] 24 months	*Numbers completing 12 months*: ALN70mg/w, 430/468 (91.9%) RIS35mg/w, 424/468 (90.6%) *24 months*: 385/403 (95.5%) and 373/395 (94.4%) *Reasons for withdrawal 12*	Not reported	*Fractures recorded as adverse events at 12 months:* ALN70mg/w 17/468 (3.6%) RIS35mg/w, 18/468 (3.8%) *Between-group difference:* Not reported *24 months:* ALN70mg/w, 23/403 (5.7%) RIS35mg/w, 25/395 (6.3%)	*Mean percent change (SD) from baseline (extracted from graph) 12 months:* ALN70mg/w, 2.25 (3.73) RIS35mg/w, 1.67 (3.71) *Between-group difference:* 0.56% (95%CI 0.03, 1.09); p=0.039 *24 months:*

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	months: ALN70mg/w, AE, 19 (4%); withdrew consent, 12 (2.5%); lost to follow-up, 2 (<1%); protocol deviation, 2 (<1%); other 3 (<1%) RIS35mg/w, AE, 29 (4.2%); withdrew consent, 6 (1.3%); lost to follow-up, 6 (1.3%); protocol deviation, 1 (<1%); other 2 (<1%) *24 months*: ALN70mg/w, AE 19, withdrew consent 12, lost to FU 2, protocol deviation 2, other 3 RIS35mg/w, AE 29, withdrew consent 6, lost to FU 6, protocol deviation 1, other 2		*Between-group difference:* Not reported	ALN70mg/w, 3.49 (5.55) RIS35mg/w, 2.53 (3.74) *Between-group difference:* 1.0% (95% CI: 0.3–1.6%); p=0.002
Hadji 2012[71] Hadji 2010[108] (ROSE) 12 months	*Numbers completing:* ZOL5mg/y, 389/408 (95%) ALN70mg/w, 172/196 (87.8%) *Reasons for withdrawal:* Overall, AEs (3.3%), withdrawal of consent (1.3%), and loss to follow-up (1.7%) ZOL5mg/y, 59/408 (14.5%) major protocol violations ALN70mg/w, 3/196 (1.5%) discontinued treatment without post-baseline measurement; 45/196 (23%) major protocol	Reports 80.9% patients were compliant with ALN therapy.	Not an outcome	Not an outcome

Trial and follow-up	Numbers completing and reasons for withdrawal	Compliance	Fracture outcomes – n/N (%) participants; reported between-group difference	FN BMD outcomes; reported between-group difference
	violations			
Reid 2009[90] (HORIZON) 12 months	*Numbers completing:* ZOL5mg/y treatment, 256/272 (94%); prevention, 129/144 (90%) RIS5mg/d - treatment, 255/273 (93%); prevention, 131/144 (91%) *Reasons for withdrawal:* ZOL5mg/y treatment, 3 had adverse event; 6 withdrew consent; 3 lost to follow-up; 3 deaths; 1 did not receive drug; prevention, 6 had adverse event; 5 withdrew consent; 3 lost to follow-up; 1 death RIS5mg/d - treatment, 3 had adverse event; 1 protocol deviation; 5 withdrew consent; 2 lost to follow-up; 3 deaths; 4 did not receive drug; prevention, 3 had adverse event; 5 withdrew consent; 4 lost to follow-up; 1 did not receive drug		Reports that the frequency of new vertebral fractures was zoledronic acid (n=5) and risedronate (n=3), with no significant difference between drug groups. Data by subgroup not reported.	*Mean percent change from baseline (SD):* ZOL5mg/y treatment, 1.45 (4.87) RIS5mg/d treatment, 0.39 (4.63) *Between-group difference:* 1.06% (95%CI 0.32 to 1.79) ZOL5mg/y prevention, 1.30 (5.05) RIS5mg/d prevention, -0.03 (5.34) *Between-group difference:* 1.33% (95%CI 0.41 to 2.25)

ALN, alendronate; BMD, bone mineral density; Ca, calcium; FN, femoral neck; IBN, ibandronate; mg/d, milligrams per day; mg/m, milligrams per month; mg/y, milligrams per year; OP, osteoporosis; PBO, placebo; RIS, risedronate; RH, relative hazard; RR, relative risk; SD, standard deviation; ZOL, zoledronate; 95%CI, 95% confidence interval

5.2.2.1 Methods for the network meta-analyses

A network meta-analysis was conducted for each of the four main fracture types, and for femoral neck bone mineral density (BMD).

Selection of evidence contributing to the network meta-analysis

For RCTs to be eligible for inclusion in the NMA the interventions were required to be assessed in line with the licensing indications. RCTs that included both licensed and unlicensed dose groups were included where outcome data for the licensed group could be isolated. RCTs that only reported results pooled across RCT groups were not included.

An assumption of the NMA is that RCTs are exchangeable in the sense that we would be prepared to treat any patient with any one of the treatments. Strictly, the RCTs included in this evidence synthesis are not exchangeable because not all of the treatments are licensed in all patient populations but the analysis follows the agreed scope.

Two RCTs reported that participants were switched from 5 mg per day alendronate to 10 mg per day after 24 months of the 36 month trial (FIT I, Black *et al.*, 1996;[57], FIT II, Cummings *et al.*, 1998[66]). A sensitivity analysis was performed to explore the impact on the results of excluding these RCTs from the analysis.

Vertebral fractures were assessed using either clinical/symptomatic (three RCTs), or morphometric/radiographic (16 RCTs) techniques, with two RCTs not stating the assessment method. A sensitivity analysis was performed to assess the impact on the results of including in the analysis only those RCTs with clinical assessment of fractures.

Femoral neck BMD data was presented either numerically or in graphical format. Nine RCTs presented results for each treatment group in graphical format while presenting the mean differences in percentage change between treatments numerically in the text. Two of the included RCTs reported data on mean differences in percentage change between treatments only. The remaining 24 RCTs presented sample estimates for each treatment group separately, with 20 reporting in numerical format and four graphically. Where both formats were provided, numerical estimates were selected as the most accurate summaries of means and variances. Given potential inaccuracy and inconsistency between the numerical and graphical sample estimates a sensitivity analysis was performed to explore the impact on the results of excluding the graphically extracted sample estimates from the analysis.

Statistical model for the network meta-analysis of fracture outcomes

The RCTs presented data in terms of the number of individuals experiencing at least one fracture. For each fracture type, r_{ik} is defined as the number of events out of the total number of participants, n_{ik}, where the participants are receiving treatment t_{ik} in arm k of trial i. The data generation process is assumed to follow a Binomial likelihood such that

$$r_{ik} \sim bin(p_{ik}, n_{ik}), \quad (1)$$

where $p_{i,k}$ represents the probability of an event in arm k of trial i $(i = 1 \ldots ns, k = 1 \ldots na)$ after follow up time f_i. For all RCTs, the number of arms included in the analysis is 2 (i.e. $na = 2$) and the number of RCTs, ns, varies according to fracture type.

To account for different trial durations, an underlying Poisson process is assumed for each trial arm, so that T_{ik} (the time until a fracture occurs in arm k of study i) follows an exponential distribution, $T_{ik} \sim exp(\lambda_{ik})$, where λ_{ik} is the event rate in arm k of study i, assumed constant over time. The probability that there are no events at time f_i is given by the survivor function, $P(T_{ik} > f_i) = \exp(-\lambda_{ik} f_i)$. For each study, i, the probability of an event in arm k after follow up time f_i can be written as

$$p_{ik} = 1 - P(T_{ik} > f_i) = 1 - \exp(-\lambda_{ik} f_i), \quad (2)$$

which is dependent on follow up time. The probabilities of fracture are non-linear functions of event rates and so were modelled using the complementary log-log link function:

$$cloglog(p_{ik}) = \log(f_i) + \mu_i + \delta_{i,1k} I_{k \neq 1}. \quad (3)$$

Here, the μ_i are trial specific baselines, representing the log-hazards of fracture in the baseline treatment, which is assumed to be arm $k = 1$ for all trials. Note that for some trials, the baseline may be an active treatment rather than placebo. The trial-specific treatment effects, $\delta_{i,1k}$, are log-hazard ratios of fracture for the treatment in arm k, relative to the baseline treatment.

As described below, two different modelling strategies were considered for the treatment effects; i) standard independent random (treatment) effects model ii) exchangeable treatment effects model i.e. class effects model where the treatment effects are assumed to arise from a common distribution according to the class of drug. The main results presented in Section 5.2.3.5. are based on the class effects model for reasons discussed below, while the results for the standard independent random effects model are provided in Appendix 7 for comparison.

Standard independent random effects model:

The trial-specific treatment effects, $\delta_{i,1k}$, were assumed to arise from a common population distribution with mean treatment effect relative to the reference treatment, which was defined as placebo for this analysis, such that

$$\delta_{i,1k} \sim N\left(d_{t_{i1}t_{ik}}, \tau^2\right), \quad (4)$$

where $d_{t_{i1}t_{ik}}$ represents the mean effect of the treatment in arm k of study i (t_{ik}) compared to the treatment in arm 1 of study i (t_{i1}) and τ^2 represents the between study variance in treatment effects (heterogeneity) which is assumed to be the same for all treatments.

The model was completed by specifying prior distributions for the parameters. Where there were sufficient sample data, conventional reference prior distributions were used:

- Trial specific baseline, $\mu_i \sim N(0, 100^2)$,
- Treatment effects relative to reference treatment, $d_{1k} \sim N(0, 100^2)$,
- Between study standard deviation of treatment effects, $\tau \sim U(0,2)$.

For both hip and wrist fracture outcomes, there were relatively few RCTs to allow Bayesian updating (i.e. estimation of parameters from the sample data alone) of the reference prior distribution for the between-study standard deviation. When prior distributions do not represent reasonable prior beliefs then, in the absence of sufficient sample data, posterior distributions will not represent reasonable posterior beliefs. Therefore, rather than using a reference prior distribution, a weakly informative prior distribution was used for the between study standard deviation such that: $\tau \sim HN(0, 0.32^2)$.

Only one RCT (ARIBON, Lester *et al.*, 2008[76]) assessed the effect of ibandronate (relative to placebo) on hip fractures. There were no fractures in the control arm and the model was unable to converge for this parameter. A weakly informative prior distribution was used for the baseline of this study (details provided in Appendix 7), whilst reference prior distributions were used for the baselines of the remaining RCTs.

Class effects model

Not all RCTs contributing wrist fracture data provide evidence about all bisphosphonates; in particular, there was no evidence about zoledronate. To allow an assessment of the uncertainty associated with zoledronate for inclusion in the economic model, a class effects model was fitted from which the predictive distribution of a new intervention in the same class can be generated. This modelling approach also has the benefit of addressing data sparsity in the hip network without the

need to use of a weakly informative prior for the baseline of ARIBON, Lester *et al.*, 2008[76] (as was required when fitting a standard independent random effects model).

A class effects model was also fitted for all fracture types. Under a class effects model, the trial-specific treatment effects are again assumed to be Normally distributed as in equation (3), but the mean effects of each treatment are assumed to be exchangeable and assumed to arise from a Normal distribution with mean, D, with variance τ_D^2:

$$d_{t_{i1}t_{ik}} \sim N(D, \tau_D^2). \quad (5)$$

The model was completed by specifying prior distributions for the parameters.

- Mean bisphosphonate effect, $D \sim N(0, 100^2)$,
- Between treatment standard deviation, $\tau_D \sim U(0,2)$.

For hip and wrist outcomes where information for some treatments was either weak or absent, a weakly informative prior was used for the between treatment standard deviation such that: $\sigma_D^2 \sim HN(0, 0.32^2)$.

Predicting effects in new RCTs

To account for heterogeneity in the effect of treatments between RCTs, results are also presented for the predictive distributions of the effect of treatment in a new (randomly chosen) study.

From equation (4), it follows that the study specific population log-hazard ratio, $\delta_{i,j}$, for study i, evaluating bisphosphonate j in reference to the control treatment can be written as

$$\delta_{i,j} = d_{1j} + \varepsilon_{ij}, \quad (6)$$

where $\varepsilon_{ij} \sim N(0, \tau^2)$. The predictive distribution for the effect of a particular bisphosphonate in a new study $\delta_{i,j}$ from the same class following, in a new study is:

$$\delta_{new,j} \sim N\left(d_{1j}, \tau^2\right) \quad (7)$$

The class effects model also allows generation of the predictive distribution of a new, randomly chosen treatment from the same class. From equation (5), it follows that the population log-hazard ratio for each treatment can be written as

$$d_{1j} = D + \xi_j, \quad (8)$$

where $\xi \sim N(0, \tau_D^2)$. Therefore, combining equations (6) and (8), the study-specific population log-hazard ratio, δ_{ij}, for study i evaluating bisphosphonate j is:

$$\delta_{ij} = D + \zeta_j + \varepsilon_{ij}, \quad (9)$$

For a new, randomly chosen bisphosphonate, the expectation is $E[\delta_{ij}] = E[D + \zeta_j + \varepsilon_{ij}] = D$, with variance:

$$V[\delta_{ij}] = V[D + \zeta_j + \varepsilon_{ij}] = \tau^2 + \tau_D^2 \quad (10)$$

Therefore, the predictive distribution for the effect of a new, randomly chosen study from the same class is:

$$\delta_{new} \sim N(D, \tau_D^2 + \tau^2), \quad (11)$$

which accounts for both between study, τ^2, and between treatment within class, τ_D^2, heterogeneity for any (including a new) treatment.

It is the predictive distribution of a new treatment within the class and the predictive distribution of a new study for a new treatment within the class that we use to characterise the uncertainty about the effect of zoledronate for hip fractures.

Statistical model for the network meta-analysis of femoral neck bone mineral density

Data for femoral neck BMD outcomes was presented in two different formats; either as the percentage change in femoral neck BMD for each treatment group, or as the mean difference in the percentage change between treatment groups. Two different data generation (i.e. likelihood) models are therefore required.

Percentage change in femoral neck BMD

The majority of RCTs presented data as the percentage change in femoral neck BMD, y_{ik} , and associated standard errors, se_{ik}, for arm k of trial i with study duration f_i years. The data generation process is assumed to follow a Normal likelihood such that

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2), \quad (12)$$

where the population variance of the mean, se_{ik}^2, is assume to be known and equal to the sample estimate. The parameters of interest, θ_{ik}, are modelled using the identity link function and, to account for differing trial lengths, study duration was included as a trial level covariate. The link function is given by:

$$\theta_{ik} = \mu_i + (\delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})f_i)I_{k\neq 1}, \quad (13)$$

where $\beta_{11} = 0$, and β_{1k} $(k = 2, .., na)$ are the treatment-specific interactions, describing the relationship between the effect of treatment on percentage change in femoral neck BMD and duration

of study. The trial baselines, μ_i , represent the percentage change in femoral neck BMD from baseline in the reference arm. The treatment effects, $\delta_{i,1k}$, represent the difference between the percentage change in the treatment group and the reference group. Assumptions about the relationship between the interaction terms are described further in the meta-regression section.

Difference between treatments in mean change in femoral neck BMD

Some RCTs provided data in terms of the mean difference in percentage change in femoral neck BMD between two treatments, defined as

$$MD_{i,1k} = y_{ik} - y_{i1}, \tag{14}$$

together with the associated standard errors of the mean difference, $v_{i,1k}$, rather than the percentage change in femoral neck BMD for individual treatments. The difference between treatments in the mean change are also assumed to be Normally distributed such that:

$$MD_{i,1k} \sim N\left(\theta'_{ik}, v_{i1k}^2\right), \tag{15}$$

where the population standard error of the difference, v_{i1k}^2, is assumed to be known and equal to the sample estimate. From the mean differences, no trial-specific effects of the baseline treatment can be estimated. The linear predictor is then given by

$$\theta'_{ik} = (\delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})f_i)I_{k\neq 1} \tag{16}$$

The study-specific treatment effects, $\delta_{i,1k}$, have the same interpretation as those from the equation (13) and thus can be combined to estimate the mean effects for each treatment, regardless of the way the data were reported.

A class effects model was assumed such that the treatment effects of the individual bisphosphonates were assumed to be exchangeable and to arise from a Normal distribution with mean, D, with variance τ_D^2:

$$d_{t_{i1}t_{ik}} \sim N(D, \tau_D^2). \tag{17}$$

The model was completed by specifying prior distributions for the parameters, using conventional reference prior distributions:

- Trial specific baseline, $\mu_i \sim N(0, 100^2)$,
- Treatment effects relative to reference treatment, $d_{1k} \sim N(0, 100^2)$,
- Between study standard deviation of treatment effects, $\tau \sim U(0,100)$.
- Mean of related treatment effects, $D \sim N(0, 100^2)$,

- Between treatment standard deviation, $\tau_D \sim U(0,100)$.

Meta-regression

Where appropriate, heterogeneity in treatment effects was explored by considering potential treatment effect modifiers. Meta-regression was used to test for interactions between the treatment effects and trial level covariates, as described in Dias *et al.*[144].

An interaction term, β, is introduced on the treatment effect by replacing

$$\tilde{\delta}_{i,1k} = \delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})(x_i - \bar{x}), \quad (18)$$

where x_i is the trial-level covariate for trial i and may represent a subgroup, continuous covariate, or baseline risk (as described in more detail below), and $\beta_{11} = 0$. The regression is centred at the mean value of the covariate across the RCTs so that the interpretation of the treatment effect is as the effect at the average value of the covariate.

Different assumptions can be made about the relationship between the interaction terms for each treatment. For the main analysis, we assume a common interaction for each treatment relative to treatment 1, such that

$$\beta_{1,t_{ik}} = b, \quad (19)$$

for $k = 2, \ldots, na$. We also considered a model in which the interaction terms for each treatment were considered to be related but not identical (i.e. exchangeable) such that:

$$\beta_{1,t_{ik}} \sim N(b, \tau_B^2). \quad (20)$$

Meta-regression on baseline risk/response

Baseline risk/response can be used as a proxy for differences in patient characteristics across trials that, may be modifiers of treatment effect, and so introduce a potential source of heterogeneity in the NMA. Adjustment for baseline risk/response was assessed using the method of Achana et. al. [145]

Dependence on baseline risk is introduced through an interaction term, so that:

$$\tilde{\delta}_{i,1k} = d_{t_{i1}t_{ik}} + \beta_{t_{i1}t_{ik}}(\mu_{iP} - \bar{\mu}_P) + \varepsilon_{i,t_{i1}t_{ik}}, \quad (21)$$

where $\varepsilon_{i,t_{i1}t_{ik}} \sim N(0, \tau^2)$. The updated study specific treatment effects, $\tilde{\delta}_{i,1k}$, are now adjusted using the `true' but unobserved baseline risk/response in the placebo arm of trial i, μ_{iP}. The coefficient, $\beta_{t_{i1}t_{ik}}$, represents the change in the treatment effect (e.g. log HR or difference between treatments in

mean change) per unit change in the baseline risk/response. The baseline risk/response is centred on $\bar{\mu}_P$, the observed mean (e.g. log HR or difference between treatments in mean change) in the placebo group, and $\beta_{11} = 0$.

For RCTs with an active treatment control, $(t_{i1} \neq P)$, there is no direct estimate of the placebo baseline risk/response. Under the consistency of evidence arising from the exchangeability assumption, the substitution $d_{t_{i1}t_{ik}} = d_{Pt_{ik}} - d_{Pt_{i1}}$ can be made, allowing equation (21) to be expressed as

$$\tilde{\delta}_{i,1k} = (d_{Pt_{ik}} - d_{Pt_{i1}}) + (\beta_{Pt_{ik}} - \beta_{Pt_{i1}})(\mu_{iP} - \bar{\mu}_P). \quad (22)$$

Although a placebo treatment may not be included in all RCTs, the assumption of exchangeability means that the treatment arms can be assumed missing at random without loss to efficacy, and the baseline risk/response in RCTs without a placebo arm can be estimated, borrowing strength from other RCTs [145].

As previously described, some RCTs report data on the mean differences in percentage change between two treatments. Under the model described in equations (15) and (16), study specific effects of the baseline treatment cannot be estimated. These RCTs still contribute to the model through estimation of the treatment effects, but do not directly contribute to estimation of the slope in the meta-regression.

Assessing inconsistency between direct and indirect evidence

Inconsistency between direct and indirect evidence arises because of an imbalance in treatment effect modifiers across treatments comparing different pairs of treatments. Consistency of evidence was assessed using the node-splitting method of Dias *et al.* [146] which separates evidence on a particular comparison into direct and indirect evidence.

In the case of fracture data, inconsistency was assessed for vertebral fractures only. For non-vertebral fractures, no indirect evidence was available. For hip and wrist fractures, an assessment of inconsistency was not performed because the direct evidence about treatment effect in the active comparator study is provided by one small study[84] with no events in each baseline arm, thereby providing imprecise evidence of treatment effect.

All analyses were conducted in the freely available software package WinBUGS [147] and R [148], using the R2Winbugs [149] interface package. Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, as modified by Brooks and Gelman [150], for two chains with different initial values. For all outcomes, a burn-in of 50,000 iterations of the Markov chain was used, with a

further 20,000 iterations retained to estimate parameters. The network meta-analyses exhibited moderate correlation between successive iterations of the Markov chain so were thinned by retaining every 10th sample.

Model fit was assessed using the total residual deviance, which provides an absolute measure of goodness-of-fit fit [151]. The total residual deviance can be compared to the number of independent data points to check whether the model provides a reasonable representation of the data. The deviance information criterion (DIC) provides a relative measure of goodness-of-fit that penalizes complexity and can be used to compare different models for the same likelihood and data [152]. Lower values of DIC are favourable, suggesting a more parsimonious model.

5.2.2.2 Results from the network meta-analyses

A summary of the data used in the NMA is provided in Appendix 7. Sections 5.2.3.5.1 – 5.2.3.5.4 present the results for each of the four fracture types. Results for femoral neck BMD are presented in Section 5.2.3.5.5. As described earlier, three sensitivity analyses were undertaken. Sensitivity Analysis 1 is presented in 5.2.3.5.6 and assesses the robustness of the results to the inclusion of RCTs that altered dosage over the study duration. Sensitivity Analysis 2, considering clinically assessed vertebral fractures is presented in 5.2.3.5.7. Sensitivity Analysis 3 is presented in 5.2.3.5.8, excluding RCTs for which femoral neck BMD results were provided in graphical format only. Results using the standard random effects model are presented in Appendix 7.

5.2.3.5.*1 Vertebral fractures, class effects model*

A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate, ibandronate 150 mg monthly and ibandronate 2.5 mg daily relative to placebo on the occurrence of vertebral fractures. Data were available from 21 RCTs, each comparing two treatments. Figure 42 presents the network of evidence for vertebral fractures.

The network provided seven direct treatment comparisons (edges in the network diagram). For the placebo versus ibandronate 2.5 mg daily comparison there is no direct evidence. The risedronate versus alendronate comparison is contributed by one small study, with a zero count in the control arm. Three contrasts were checked for inconsistency between direct and indirect evidence. None of the comparisons showed significant evidence of inconsistency, as assessed using Bayesian p-values (Figure 46).

Figure 42: Vertebral fractures, network of evidence.

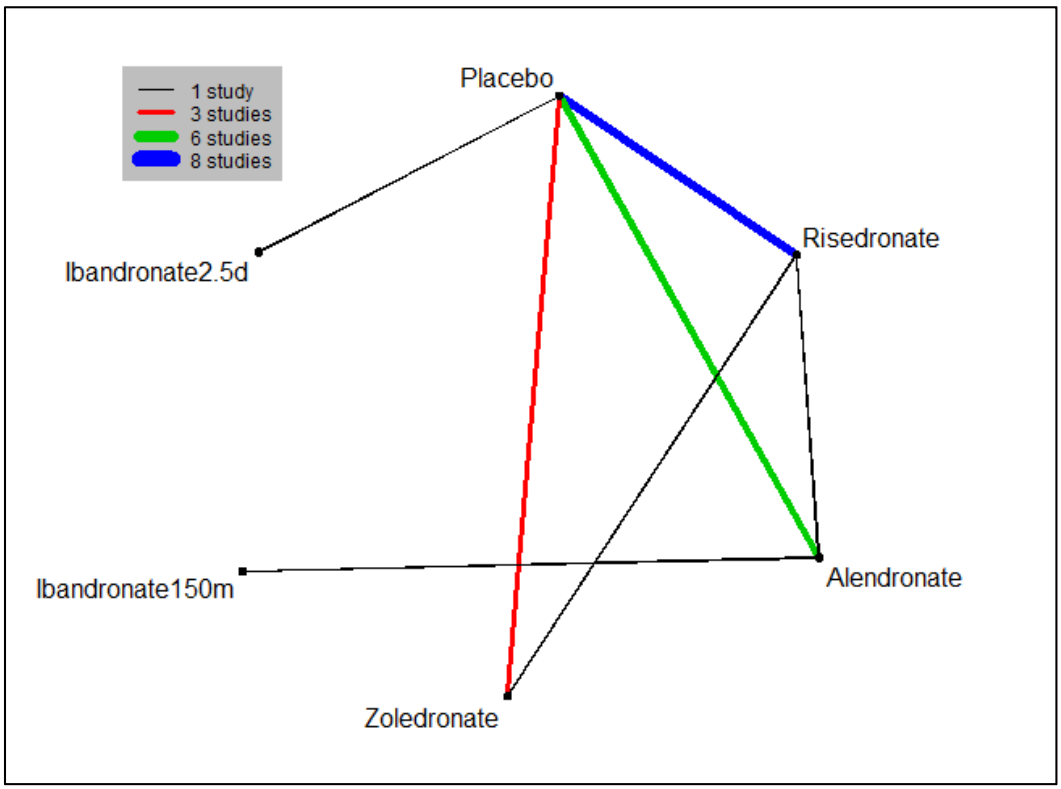


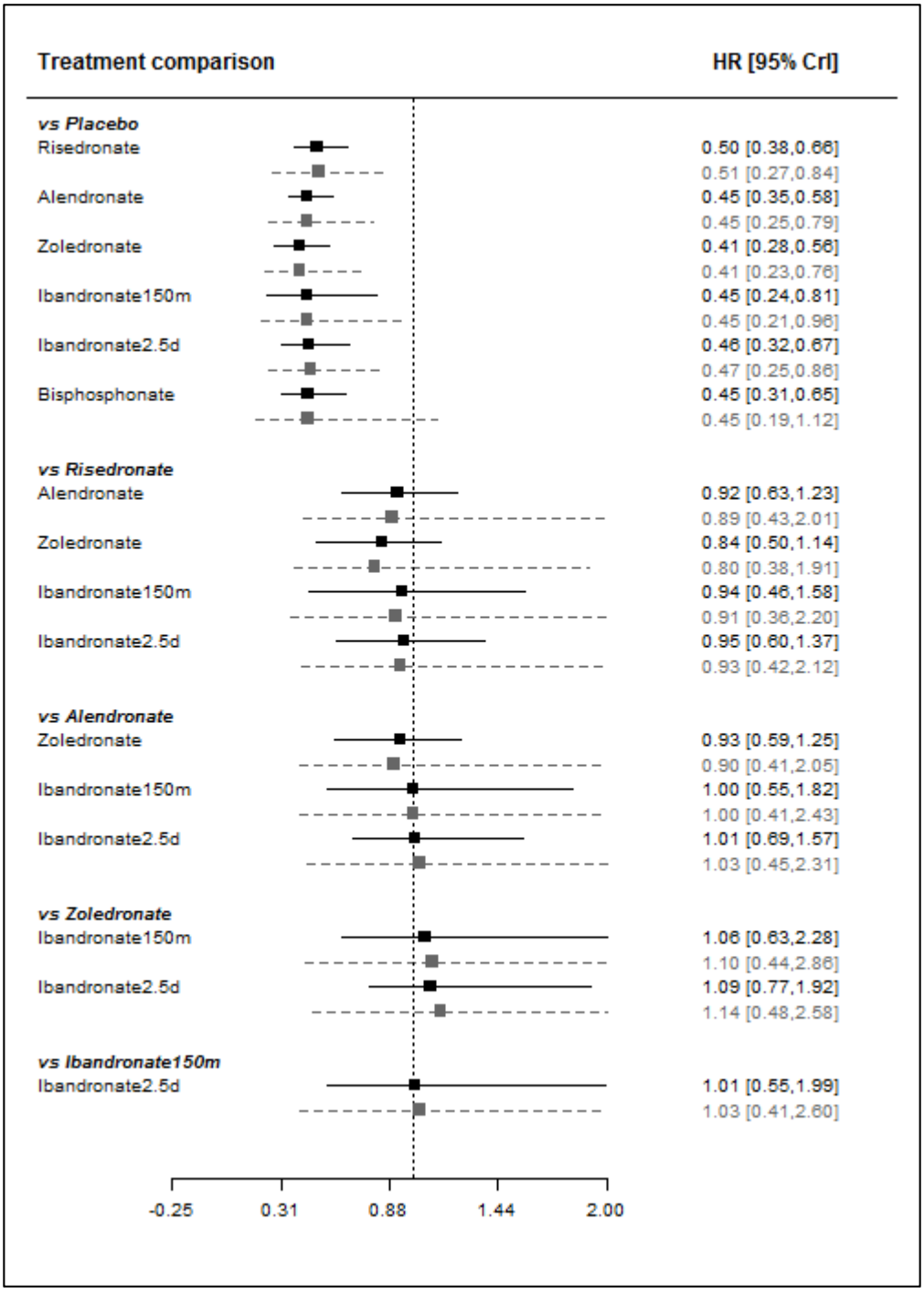
Figure 43 presents the effects of each treatment relative to placebo. The probabilities of treatment rankings are presented in Figure 44. The model fitted the data well, with a total residual deviance of 41.05 being close to the number of data points included in the analysis, 42. The deviance information criterion (DIC) was 69.28. The between study standard deviation was estimated to be 0.19 (95% CrI: 0.01, 0.49), implying mild heterogeneity in treatment effects between RCTs.

The between treatment standard deviation was estimated to be 0.18 (95% CrI: 0.01, 0.86), which is indicative of mild heterogeneity in treatment effects between treatments (i.e., the effects of the bisphosphonates are relatively similar) but with considerable uncertainty.

All treatments were associated with beneficial treatment effects relative to placebo, and all treatment effects were statistically significant at a conventional 5% level. Zoledronate was associated with the greatest effect, HR 0.41 (95% CrI: 0.28, 0.56), and was most likely to be the most effective treatment (probability 0.44 of being the most effective). Pairwise comparisons between treatments indicated that no active treatments are significantly more effective than other active treatments. The hazard ratio for a randomly chosen study for a new bisphosphonate is 0.45 (95% CrI: 0.19, 1.12), allowing for both between study and between treatment heterogeneity.

Figure 45 presents the relationship between baseline risk and treatment effect assuming a common interaction for each treatment. The model fitted the data well, with a total residual deviance of 41.11 (compared to 42 data points). . The between study standard deviation was estimated to be 0.21 (95% CrI: 0.02, 0.57) and the between treatment standard deviation was estimated to be 0.18 (95% CrI: 0.01, 0.92). The between study standard deviation from fitting a random effects model to the placebo baseline data was 1.23 (95% CrI: 0.86, 1.90), indicating substantial heterogeneity between RCTs. However, there was no evidence for an interaction between baseline risk and treatment effect, with the interaction term estimated to be 0.02 (95% CrI: -0.25, 0.22). In fact, including baseline risk did not improve the fit of the model to the data according to a comparison of DICs (70.53 versus 69.28), and actually increased the estimate of the between-study standard deviation of the treatment effect. Exchangeable and related treatment-specific interactions were also considered. The model did not provide a better fit to the data, DIC 71.50.

Figure 43: Vertebral fractures, class effects model. Hazard ratios and 95% credible intervals.



Note: mean effects estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Figure 44: Vertebral fractures, class effects model. Probability of treatment rankings.

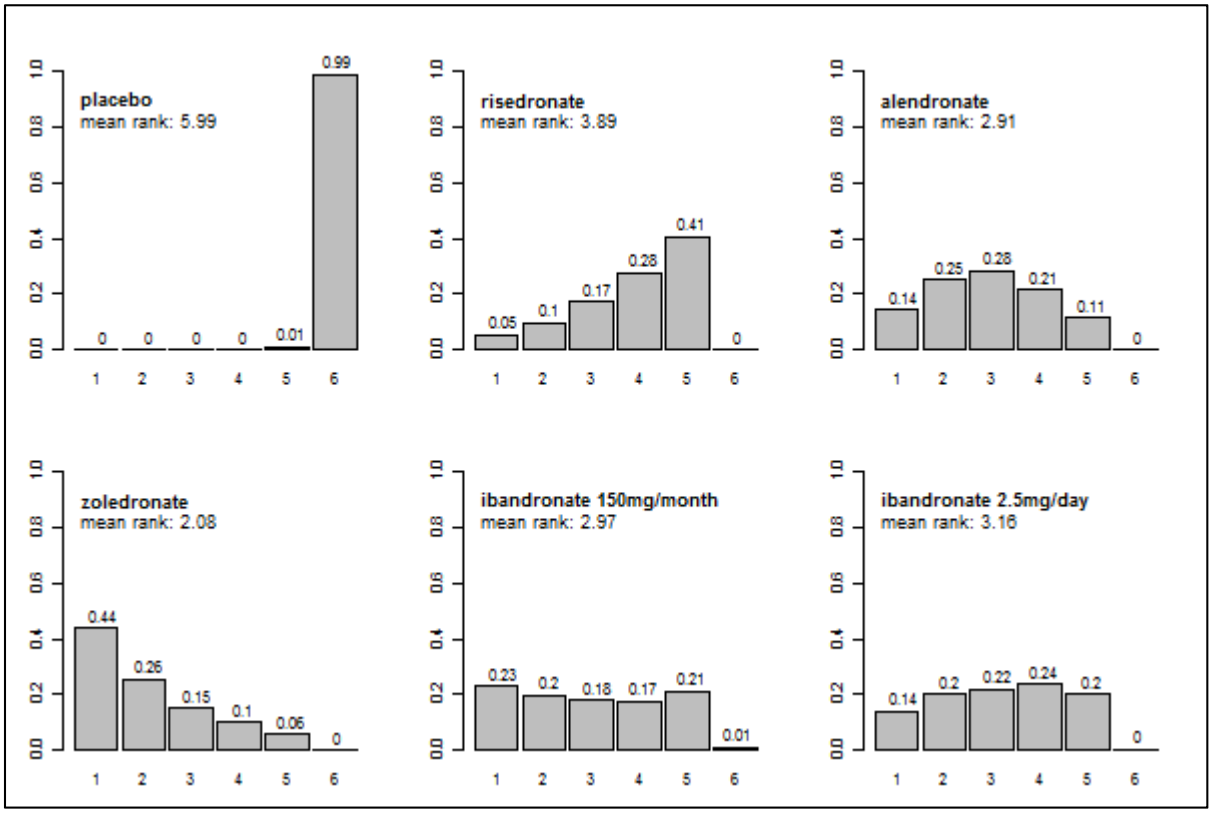
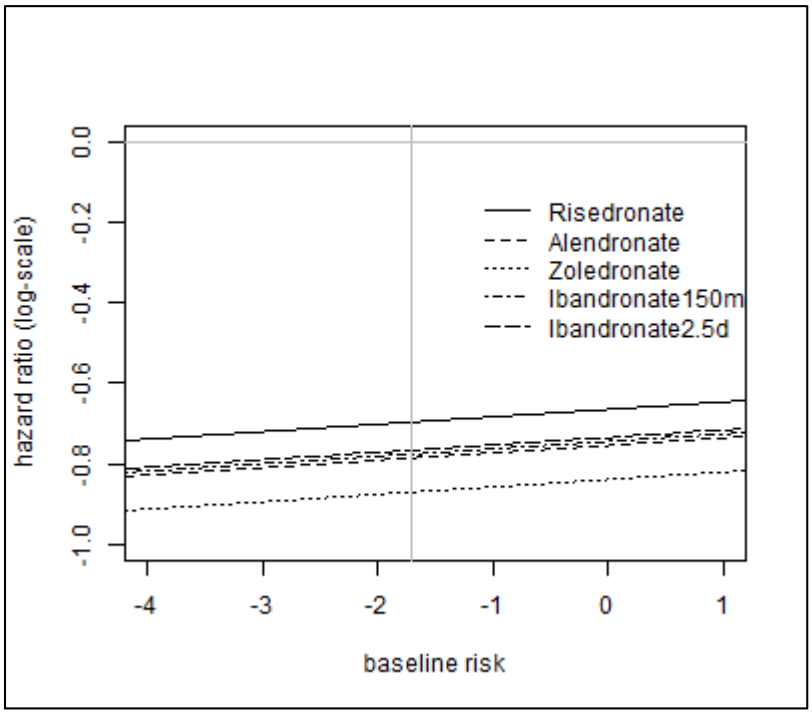
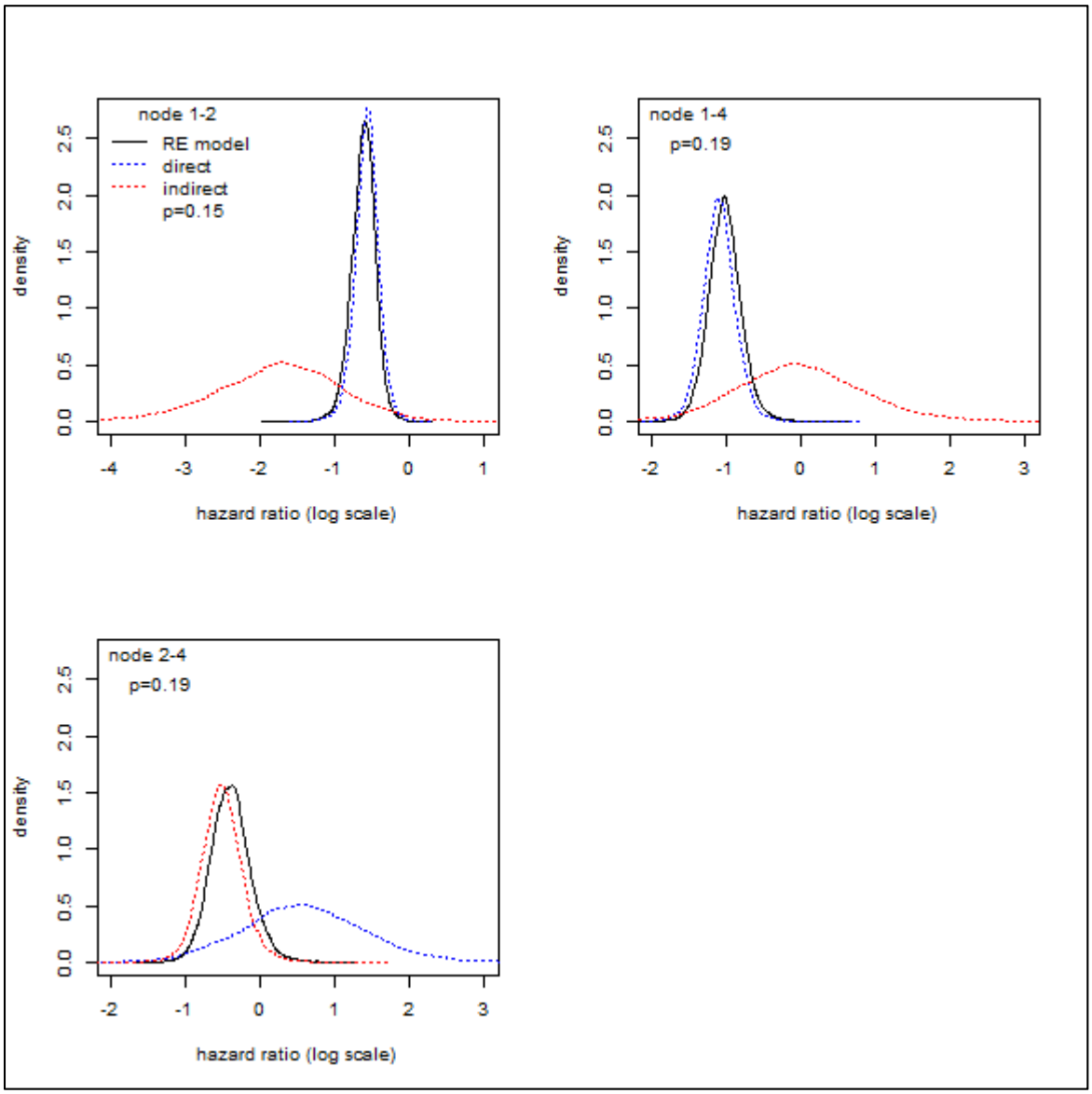


Figure 45: Vertebral fractures, class effects model. Relationship between baseline risk of vertebral fracture and treatment effects.



Note: vertical line represents mean baseline risk.

Figure 46: Vertebral fractures, class effects model. Assessing inconsistency using node splitting.

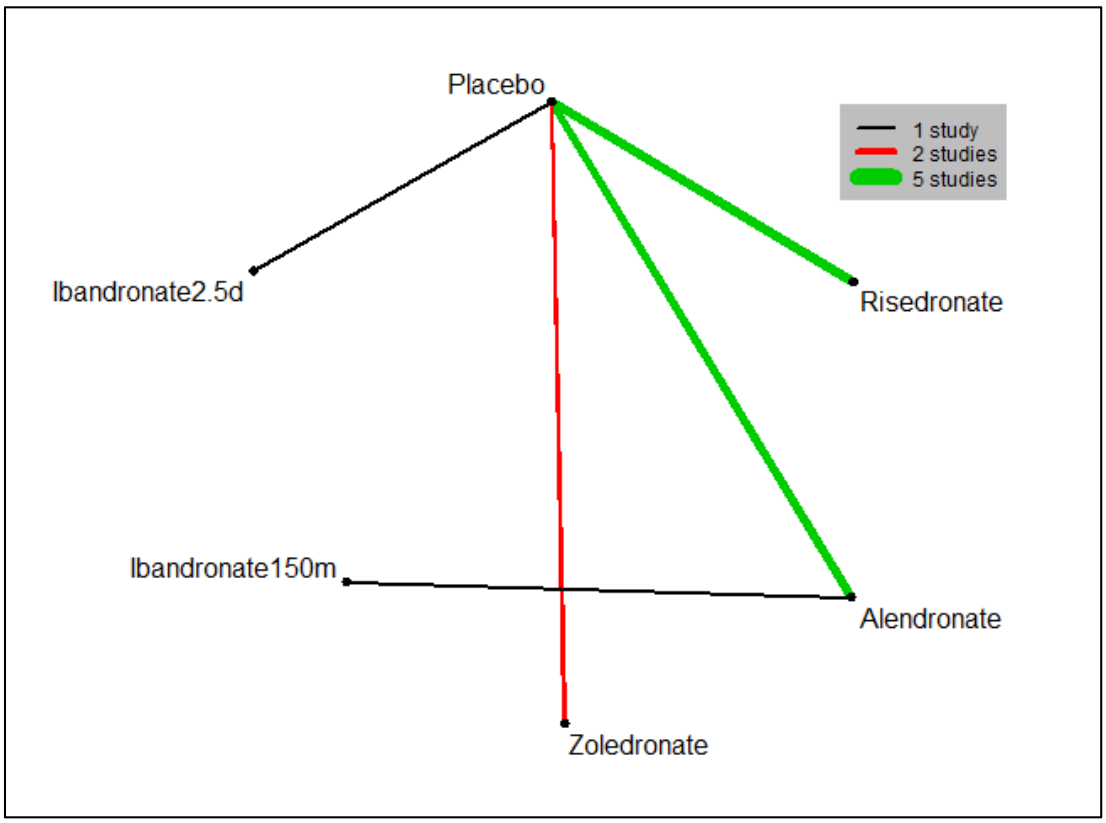


Note: comparisons from left to right, top to bottom; node 1-2: placebo-risedronate, node 1-4: placebo-zoledronate, node 2-4: risedronate-zoledronate.

5.2.3.5.*2 Non-vertebral fractures, class-effects model*

A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate, ibandronate 150 mg monthly and ibandronate 2.5 mg daily relative to placebo on the occurrence of non-vertebral fractures. Data were available from 14 RCTs, each comparing two treatments. Figure 47 presents the network of evidence for non-vertebral fractures.

Figure 47: Non-vertebral fractures, network of evidence.



Since no indirect evidence was provided by the network an assessment of inconsistency was not performed. Figure 48 presents the effects of each treatment relative to placebo. The probabilities of treatment rankings are presented in Figure 49. The model fitted the data well, with a total residual deviance of 22.80 compared to the number of data points included in the analysis, 28. The DIC was 42.32. The between study standard deviation was estimated to be 0.08 (95% CrI: 0.00, 0.31), implying mild heterogeneity in treatment effects between RCTs.

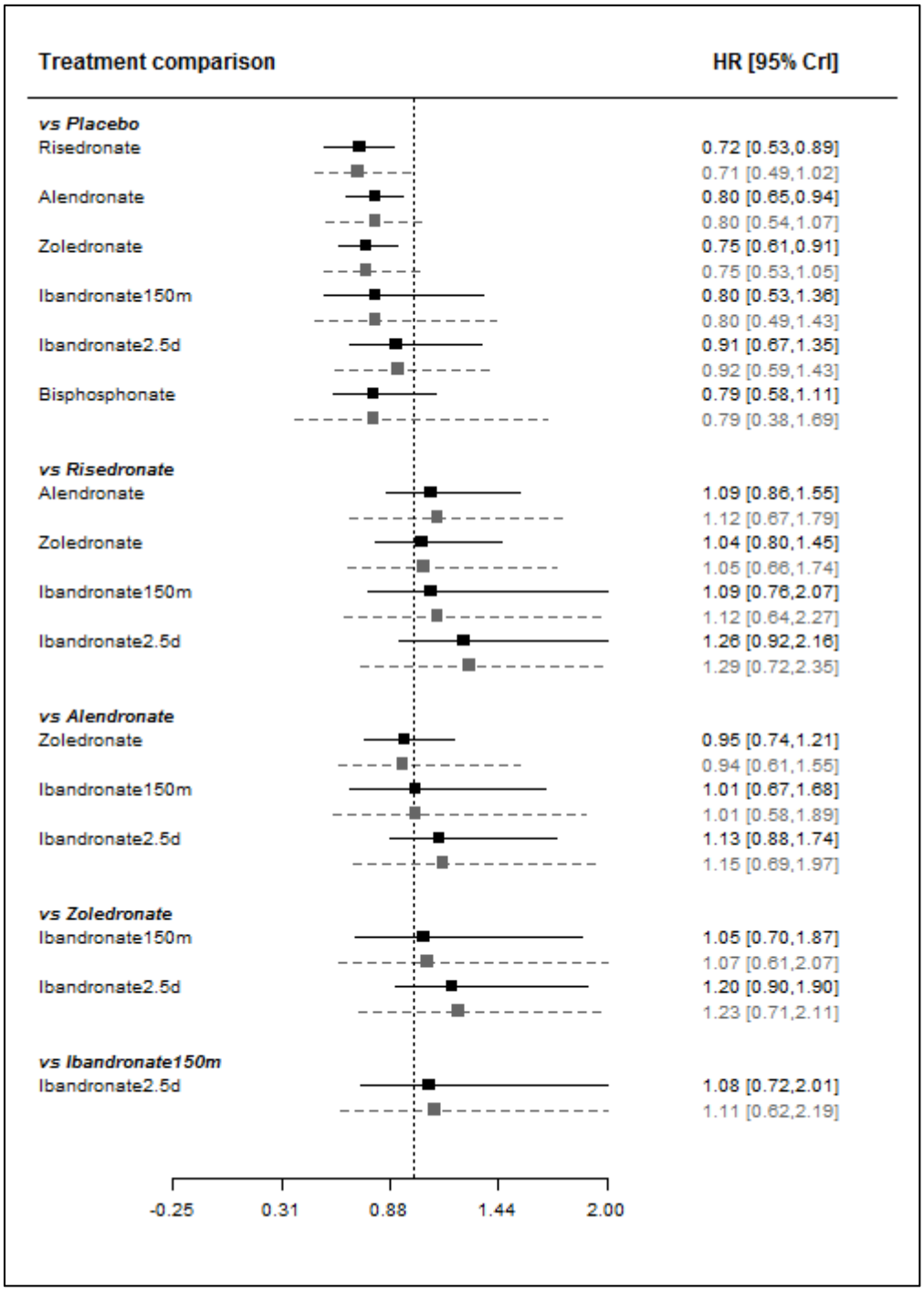
The between treatment standard deviation was estimated to be 0.17 (95% CrI: 0.01, 0.80), which is indicative of mild heterogeneity in treatment effects between treatments (i.e., the effects of the bisphosphonates are relatively similar) but with considerable uncertainty.

All treatments were all associated with beneficial treatment effects relative to placebo, with risedronate, alendronate and zoledronate being statistically significant at a conventional 5% level. Risedronate was associated with the greatest effect, HR 0.72 (95% CrI: 0.53, 0.89), and was most likely to be the most effective treatment (probability 0.46 of being the most effective). No active treatment s statistically significantly more effective than other active treatment. The hazard ratio for a randomly chosen study for a new bisphosphonate is 0.79 (95% CrI: 0.38, 1.69), allowing for both between study and between treatment heterogeneity.

Note: most efficacious =1, least efficacious = 6.

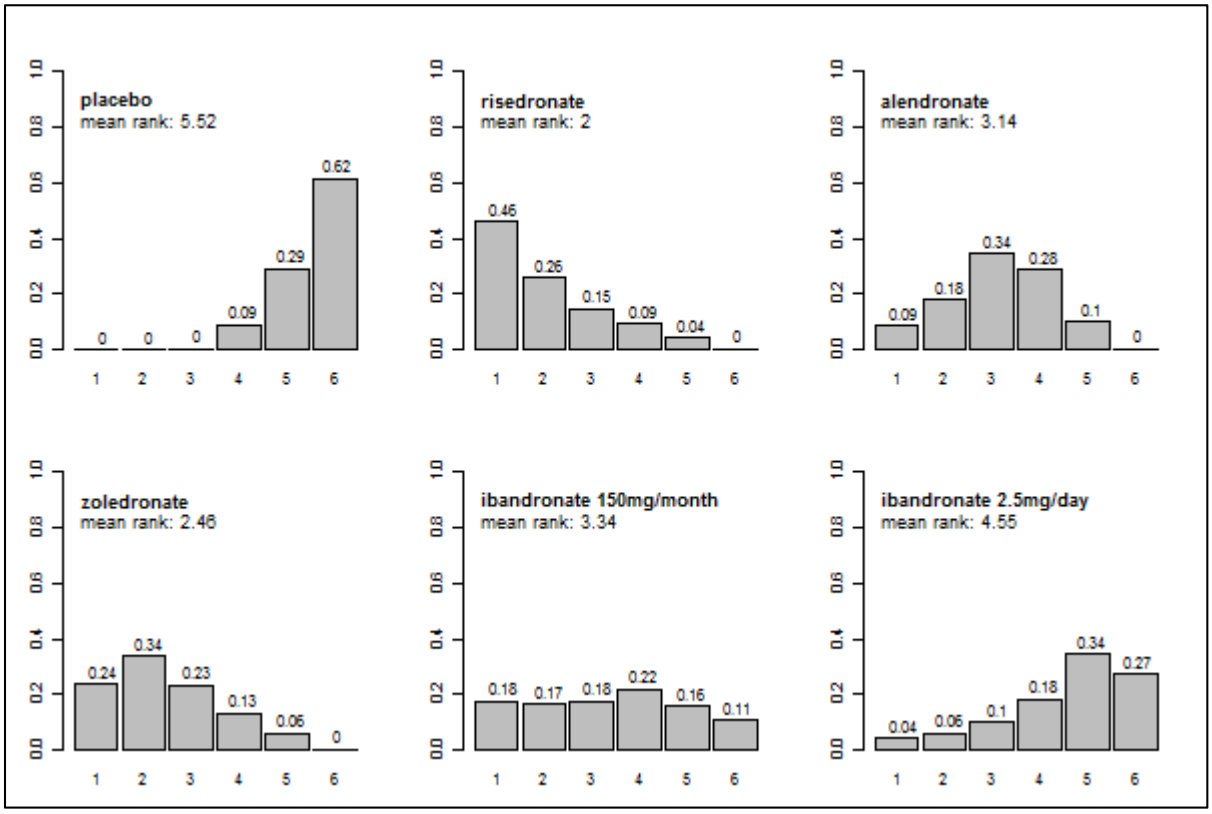
Figure 50 presents the relationship between baseline risk and treatment effect assuming a common interaction for each treatment. The model fitted the data well, with a total residual deviance of 23.65(compared to 28 data points). The between study standard deviation was estimated to be 0.11 (95% CrI: 0.01, 0.37) and the between treatment standard deviation was estimated to be 0.17 (95% CrI: 0.01, 0.81). The between study standard deviation from fitting a random effects model to the placebo baseline data was 0.48 (95% CrI: 0.32, 0.83), indicating moderate heterogeneity between RCTs. However, there was no evidence for an interaction between baseline risk and treatment effect, with the interaction term estimated to be -0.07 (95% CrI: -0.44, 0.22). In fact, including baseline risk did not improve the fit of the model to the data according to a comparison of DICs 44.27 versus 44.32), and actually increased the estimate of the between-study standard deviation of the treatment effect. Exchangeable and related treatment-specific interactions were also considered. The model did not provide a better fit to the data, DIC 45.84.

Figure 48: Non-vertebral fractures, class effects model. Hazard ratios and 95% credible intervals.



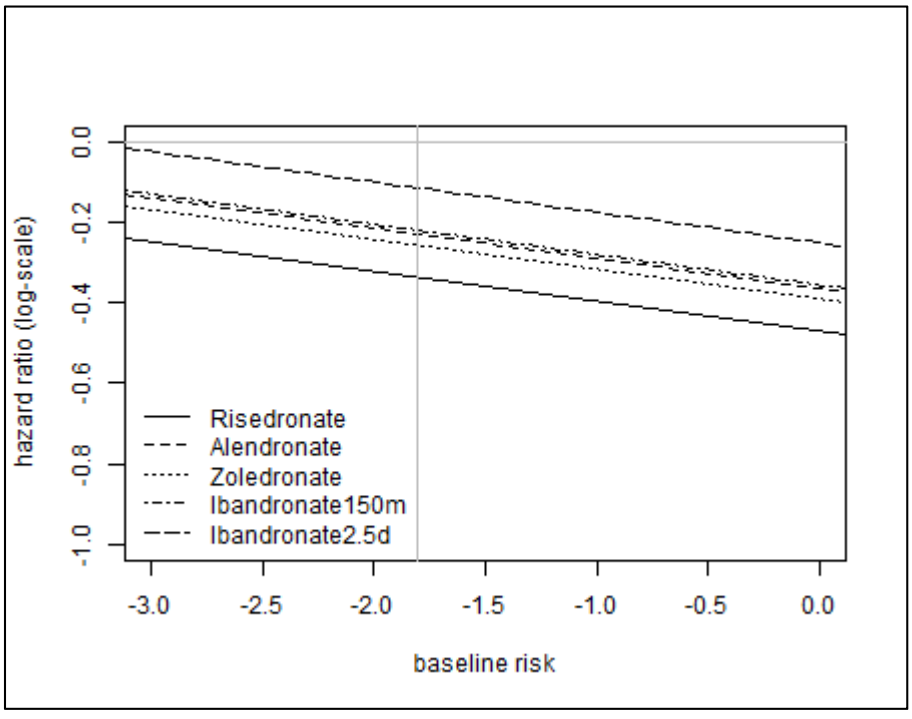
Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Figure 49: Non-vertebral fractures, class effects model. Probability of treatment rankings



Note: most efficacious =1, least efficacious = 6.

Figure 50: Non-vertebral fractures, class effects model. Relationship between baseline risk of non-vertebral fracture and treatment effects.

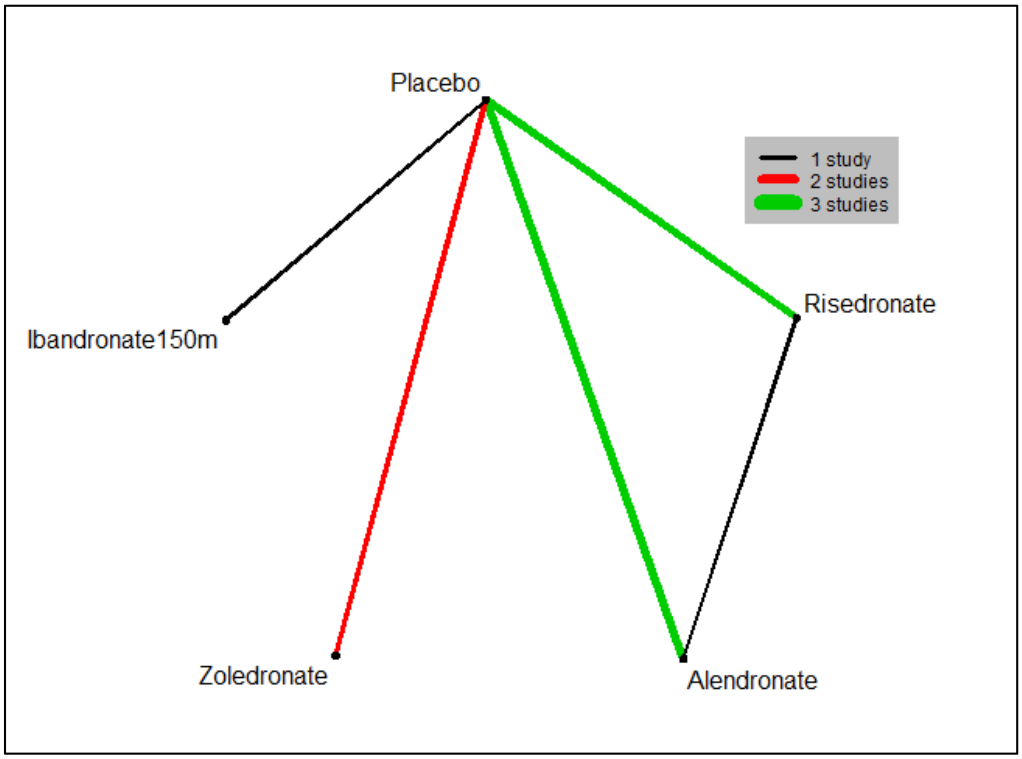


Note: vertical line represents mean baseline risk.

5.2.3.5.3 Hip fractures, class effects model

A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate and ibandronate 150m relative to placebo on the occurrence of hip fractures. Data were available from 10 RCTs, each comparing two treatments. Figure 51 presents the network of evidence for hip fractures.

Figure 51: Hip fractures, network of evidence.



Due to the limited power of indirect evidence, assessment for inconsistency was not performed.

Figure 52 presents the effects of each treatment relative to placebo. The probabilities of treatment rankings are presented in Figure 53. The model fitted the data well, with a total residual deviance of 18.46 being close to the total number of data points included in the analysis, 18. The DIC was 33.82. The between study standard deviation was estimated to be 0.43 (95% CrI: 0.23, 0.74), implying moderate heterogeneity in treatment effects between RCTs.

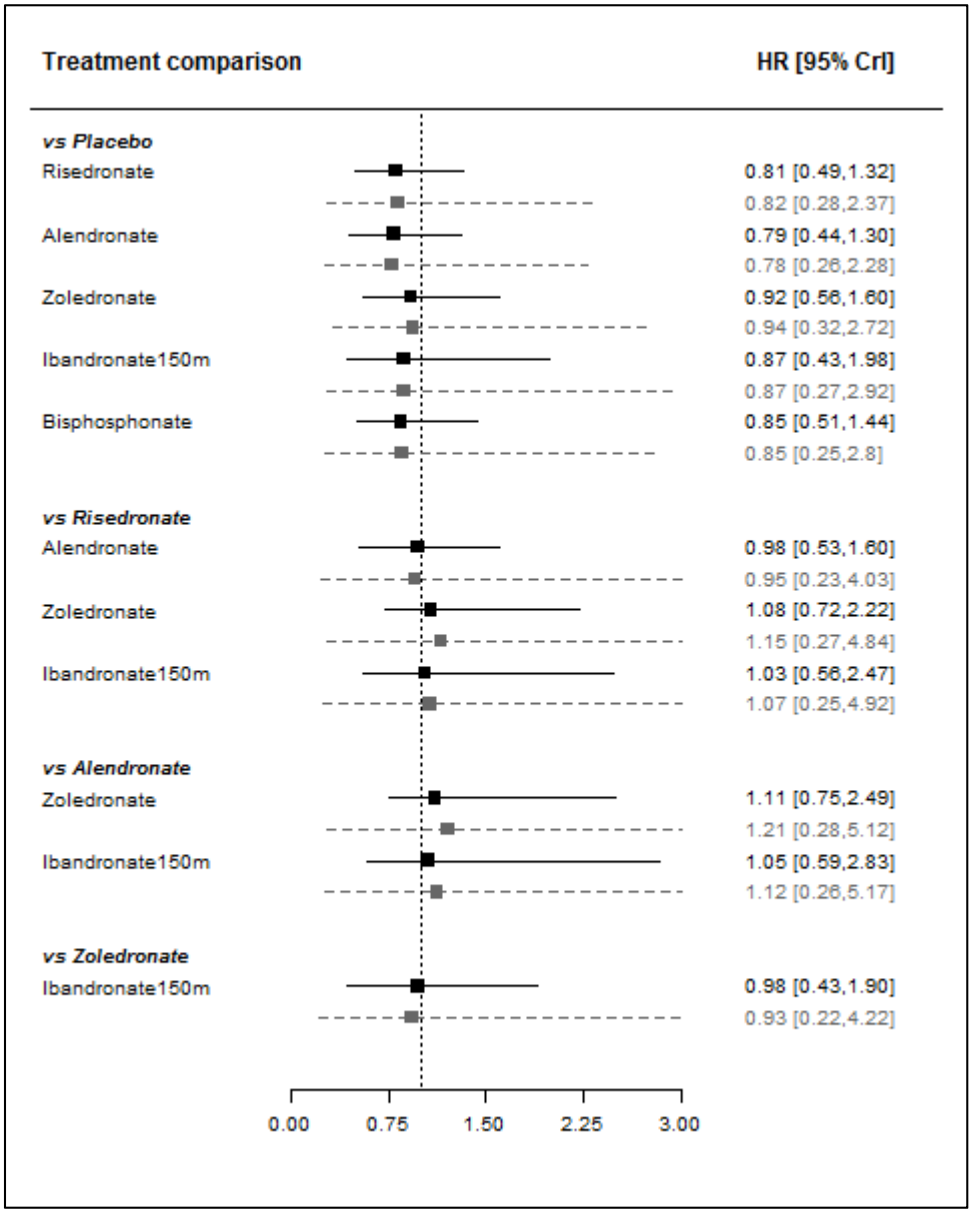
The between treatment standard deviation was estimated to be 0.19 (95% CrI: 0.01, 0.61), which is indicative of mild heterogeneity in treatment effects between treatments (i.e., the effects of the bisphosphonates are relatively similar) but with reasonable uncertainty.

All treatments were all associated with beneficial treatment effects relative to placebo, although the treatment effects were not statistically significant at a conventional 5% level. Alendronate was associated with the greatest effect, with HR of 0.79 (95% CrI: 0.44, 1.30) and was most likely to be

the most effective treatment (probability 0.36 of being the most effective). The hazard ratio for a randomly chosen study for a new bisphosphonate is 0.85 (95% CrI: 0.26, 2.77).

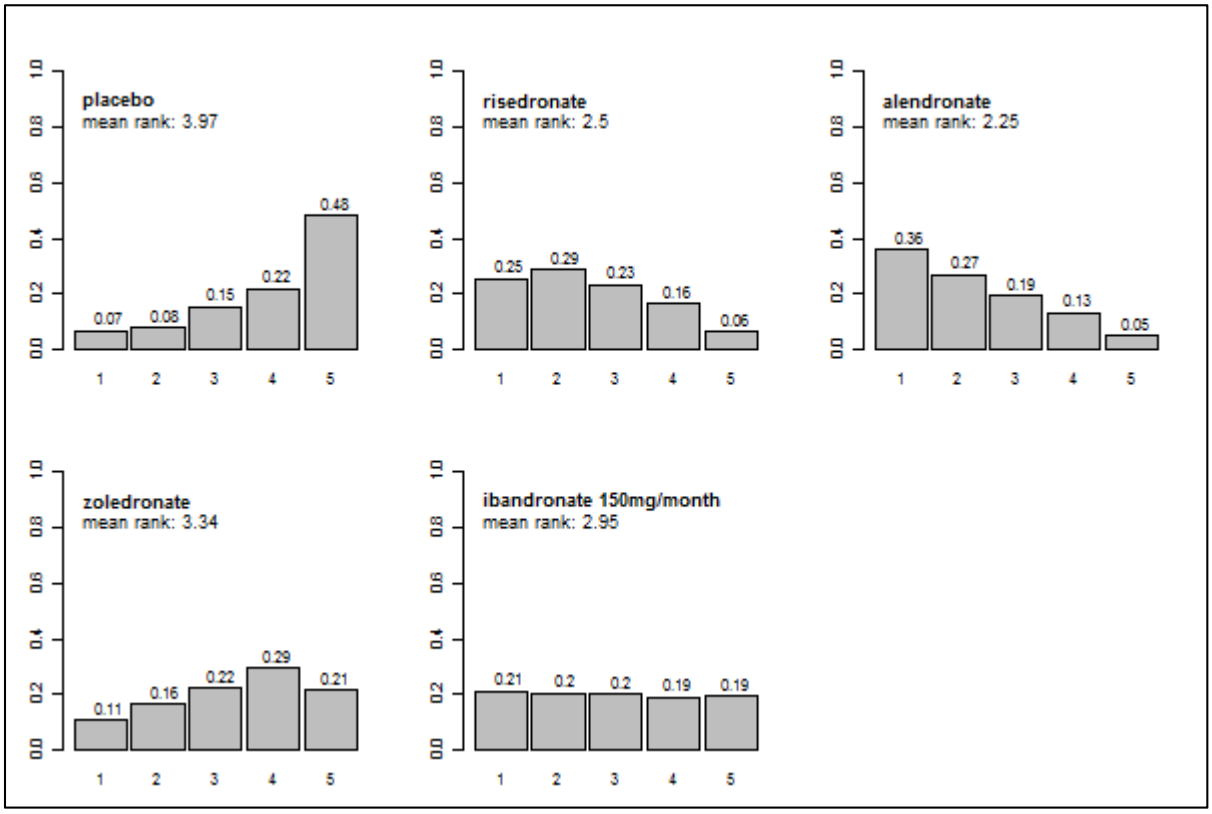
Figure 54 presents the relationship between baseline risk and treatment effect assuming a common interaction for each treatment. For the model using standard reference priors there was evidence of poor convergence, and so weakly informative priors were used for placebo arms of two RCTs; ARIBON [76] and Muscoso [84]. The model fitted the data well, with a total residual deviance of 18.78 (compared to 18 data points). The between study standard deviation was estimated to be 0.40 (95% CrI: 0.06, 0.75) and the between treatment standard deviation was estimated to be 0.19 (95% CrI: 0.01, 0.63). The between study standard deviation from fitting a random effects model to the placebo baseline data was 0.46 (95% CrI: 0.23, 1.05), indicating moderate heterogeneity between RCTs. However there was no evidence for an interaction between baseline risk and treatment effect, with the interaction term estimated to be 0.43 (95% CrI: -0.79, 1.67). In fact, including baseline risk did not improve the fit of the model to the data according to a comparison of DICs (33.48 versus 33.82), and actually increased the estimate of the between-study standard deviation of the treatment effect. Exchangeable and related treatment-specific interactions were also considered but did not provide a better fit to the data.

Figure 52: Hip fractures, class effects model. Hazard ratios and 95% credible intervals.



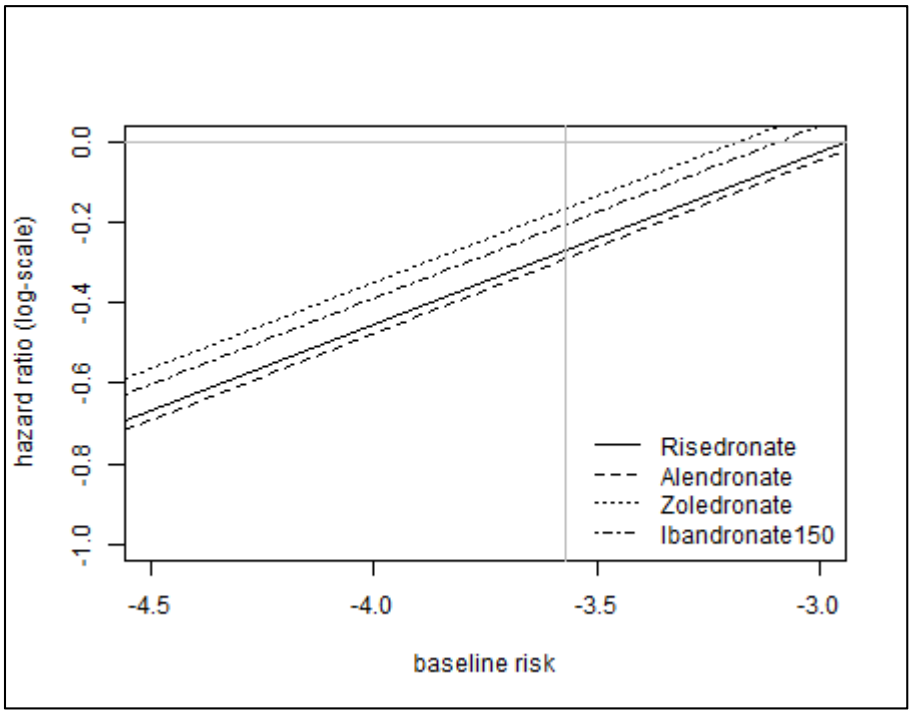
Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Figure 53: Hip fractures, class effects model. Probability of treatment rankings



Note: most efficacious =1, least efficacious = 6.

Figure 54: Hip fractures, class effects model. Relationship between baseline risk of hip fracture and treatment effects

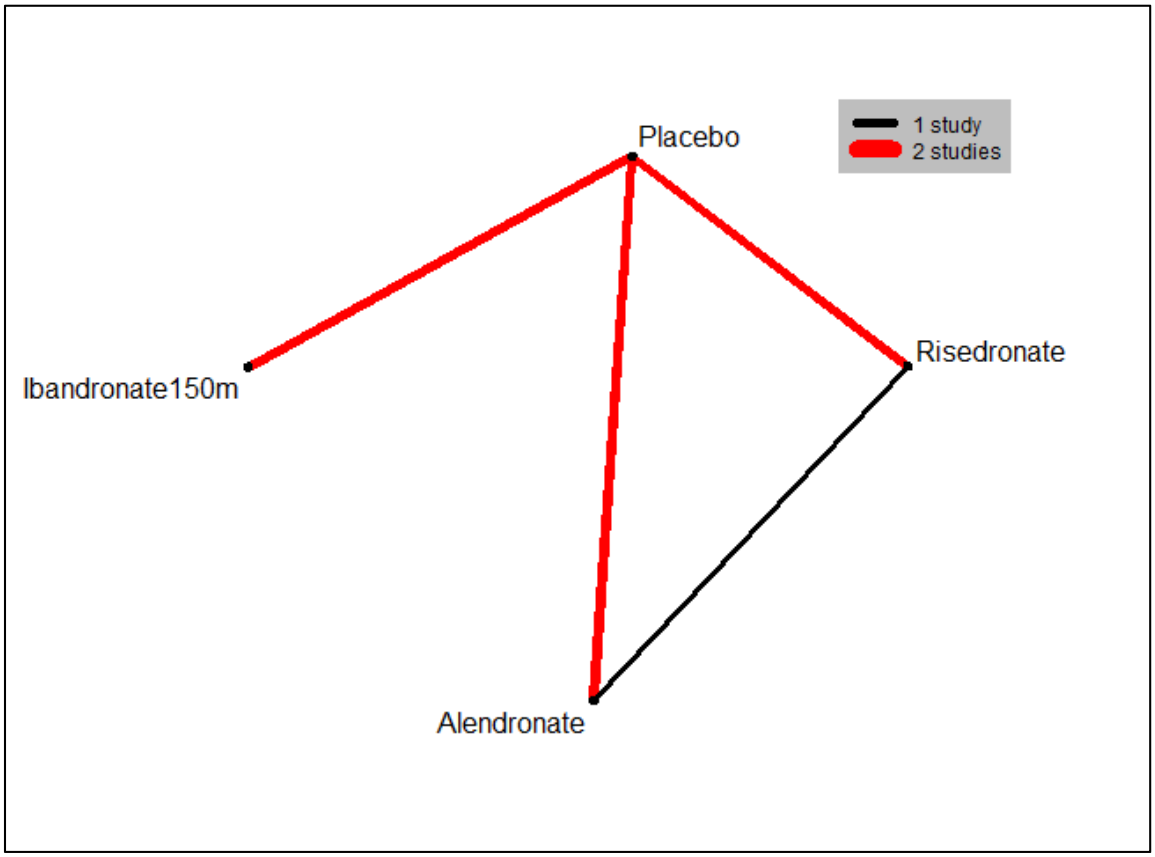


Note: vertical line represents mean baseline risk.

5.2.3.5.4 Wrist fractures, class effects model

A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate and ibandronate 150m relative to placebo on the occurrence of wrist fractures. Data were available from 7 RCTs, each comparing two treatments. Figure 55 presents the network of evidence for wrist fractures.

Figure 55: Wrist fractures, network of evidence



Due to the limited indirect evidence, an assessment for inconsistency was not performed.

Figure 56 presents the effects of each treatment relative to placebo. The probabilities of treatment rankings are presented in Figure 57. The model fitted the data well, with a total residual deviance of 13.32 being close to the total number of data points included in the analysis, 12. The DIC was 23.23. The between study standard deviation was estimated to be 0.28 (95% CrI: 0.03, 0.66), implying mild to moderate heterogeneity in treatment effects between RCTs.

The between treatment standard deviation was estimated to be 0.17 (95% CrI: 0.01, 0.62), which is indicative of mild heterogeneity in treatment effects between treatments (i.e., the effects of the bisphosphonates are relatively similar) but with reasonable uncertainty.

All treatments were all associated with beneficial treatment effects relative to placebo, although the treatment effects were not statistically significant at a conventional 5% level. Risedronate was associated with the greatest effect, with HR of 0.77 (95% CrI: 0.39, 1.28) and was most likely to be the most effective treatment (probability 0.42 of being the most effective). No active treatment was statistically significantly more effective than other active treatment. The hazard ratio for a randomly chosen study for a new bisphosphonate was 0.81(95% CrI: 0.28, 2.34).

Figure 58 presents the relationship between baseline risk and treatment effect assuming a common interaction for each treatment. For the model using standard reference priors there was evidence of poor convergence, and so weakly informative priors were used for placebo arms of two RCTs; McClung [81] and Muscoso [84]. The model fitted the data well, with a total residual deviance of 15.21 (compared to 12 data points). The between study standard deviation was estimated to be 0.35 (95% CrI: 0.04, 0.75) and the between treatment standard deviation was estimated to be 0.17 (95% CrI: 0.01, 0.61). The between study standard deviation from fitting a random effects model to the placebo baseline data was 0.44 (95% CrI: 0.12, 1.52), indicating moderate heterogeneity between RCTs. However, there was no evidence for an interaction between baseline risk and treatment effect, with the interaction term estimated to be -0.40 (95% CrI: -2.58, 1.38). In fact, including baseline risk did not improve the fit of the model to the data according to a comparison of DICs (25.85 versus 23.23), and actually increased the estimate of the between-study standard deviation of the treatment effect. Exchangeable and related treatment-specific interactions were also considered but did not provide a better fit to the data.

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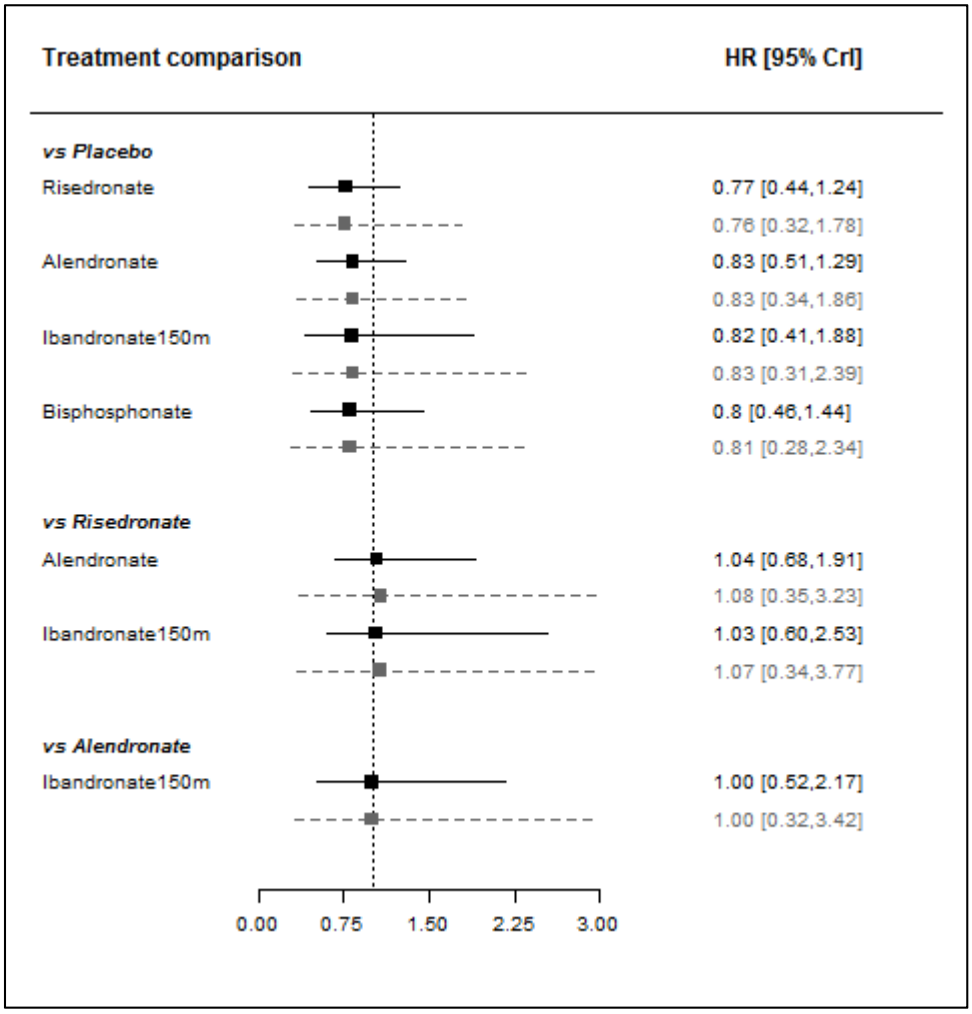
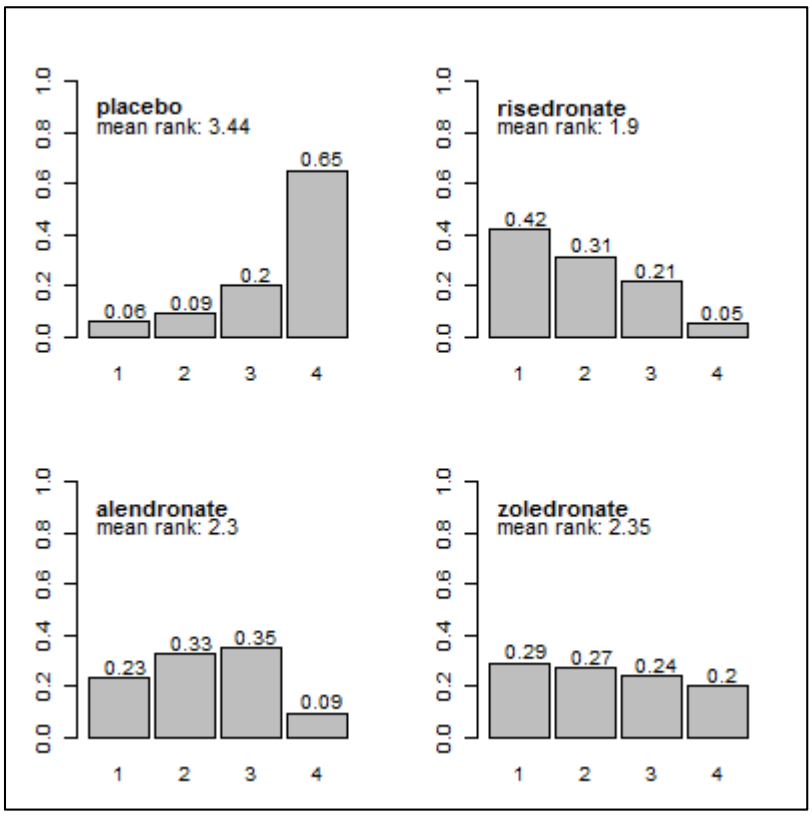
Figure 56: Wrist fractures, class effects model. Hazard ratios and 95% credible intervals



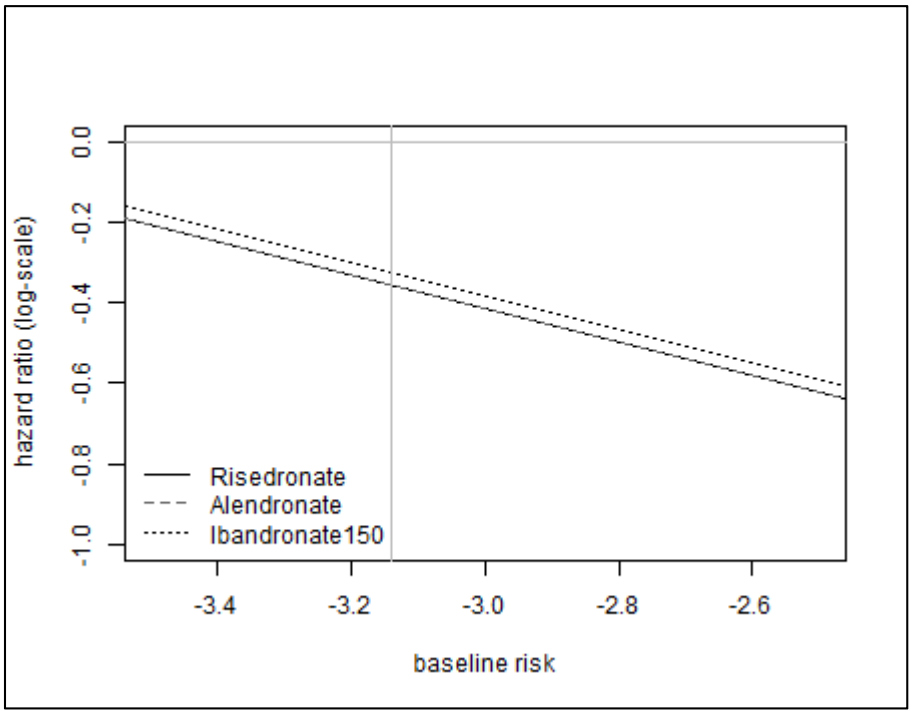
Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Figure 57: Wrist fractures, class effects model. Probability of treatment rankings



Note: most efficacious =1, least efficacious = 6.

Figure 58: Wrist fractures, class effects model. Relationship between baseline risk and treatment effects



Note: vertical line represents mean baseline risk.

5.2.3.5.5 Femoral neck bone mineral density, class effects model

A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate, ibandronate 2.5 mg daily, ibandronate 150 mg monthly and ibandronate 3ml every 3 months iv relative to placebo on the percentage change in femoral neck BMD. Data were available from 35 RCTs, each comparing two treatments.

An assessment of inconsistency between direct and indirect evidence is presented in Figure 66. The network provided 21 direct treatment comparisons (edges in the network diagram). For 12 of these comparisons there is no direct evidence, leaving nine treatment comparisons to assess for consistency.

Figure 59 presents the network of evidence for femoral neck BMD. Nine RCTs presented summary statistics for each treatment group in graphical format while presenting the mean differences in percentage change in femoral neck BMD between treatments numerically in the text. A comparison of the numerical results and the graphically extracted results is presented in Figure 60, showing generally good but not identical correspondence between the two sample estimates.

An assessment of inconsistency between direct and indirect evidence is presented in Figure 66. The network provided 21 direct treatment comparisons (edges in the network diagram). For 12 of these comparisons there is no direct evidence, leaving nine treatment comparisons to assess for consistency.

Figure 59: BMD, network of evidence

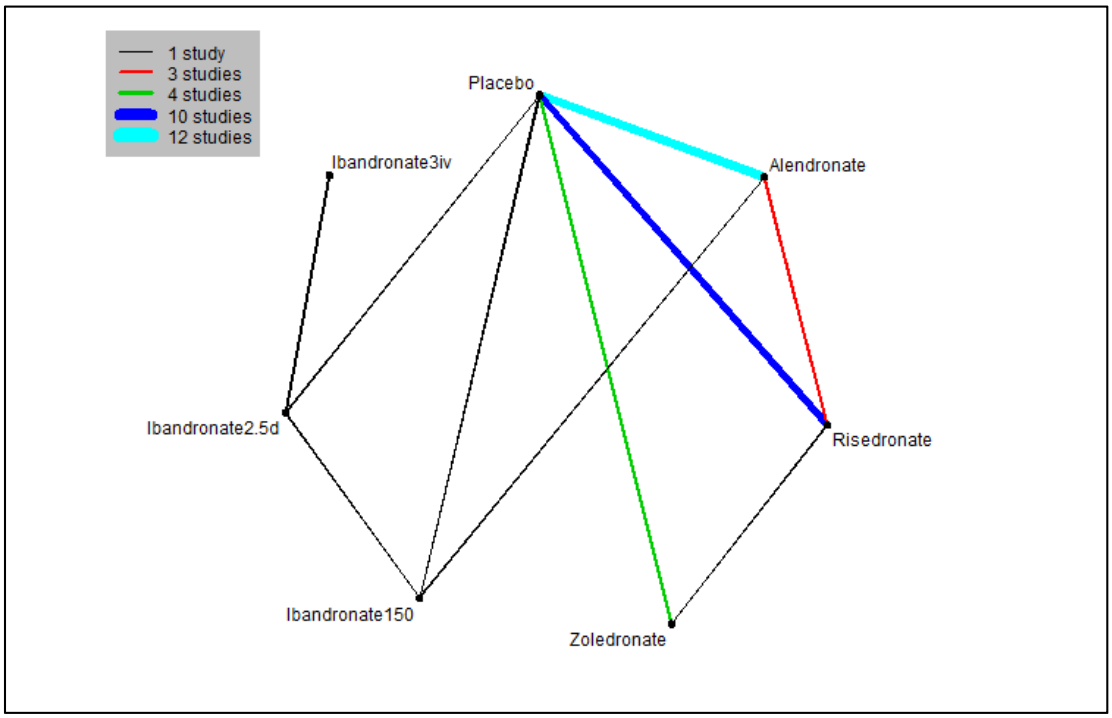


Figure 60: Percentage change in femoral neck BMD, comparison of reported versus computed (from graph estimates) values.

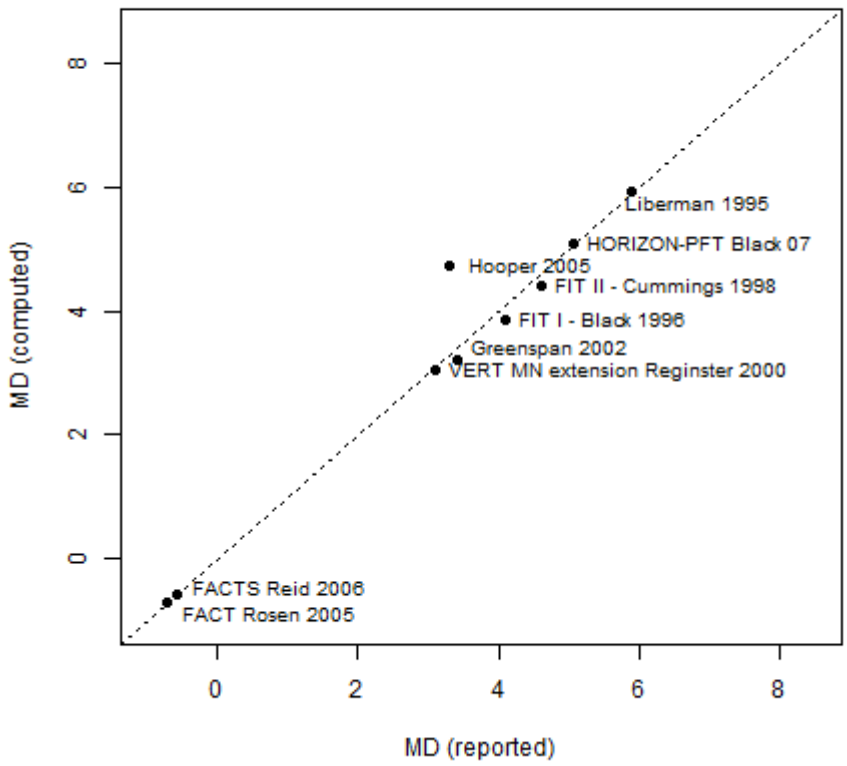


Figure 61 presents the effects of each treatment relative to placebo. The probabilities of treatment rankings are presented in Figure 62. The model fitted the data well, with a total residual deviance of 53.65 being close to the number of data points included in the analysis, 59. The DIC was 96.5. The between study standard deviation was estimated to be 0.53 (95% CrI: 0.30, 0.86), implying moderate heterogeneity in treatment effects between RCTs.

The between treatment standard deviation was estimated to be 0.56 (95% CrI: 0.19, 1.70), which is indicative of moderate heterogeneity in treatment effects between RCTs (i.e., the effects of the bisphosphonates are more dissimilar) but with considerable uncertainty.

The estimated interaction term for duration of study, assuming a common interaction for each treatment, was 0.89 (95% CrI: 0.48, 1.18) and the treatment effects are plotted against study duration in Figure 63. The estimated interaction term implies that treatment effects increase with duration of study. Exchangeable and related treatment-specific interactions were also considered. The model did not provide a better fit to the data,(DIC 97.36).

All treatments were all associated with a beneficial effect relative to placebo, and all treatment effects were statistically significant at a conventional 5% level. Zoledronate was associated with the greatest effect, treatment effect 3.21 (95% CrI: 2.52, 3.86), and was most likely to be the most effective treatment (probability 0.48 of being the most effective). The treatment effect for a randomly chosen study for a new bisphosphonate is 2.79 (95% CrI: 0.72, 4.75), allowing for both between study and treatment heterogeneity.

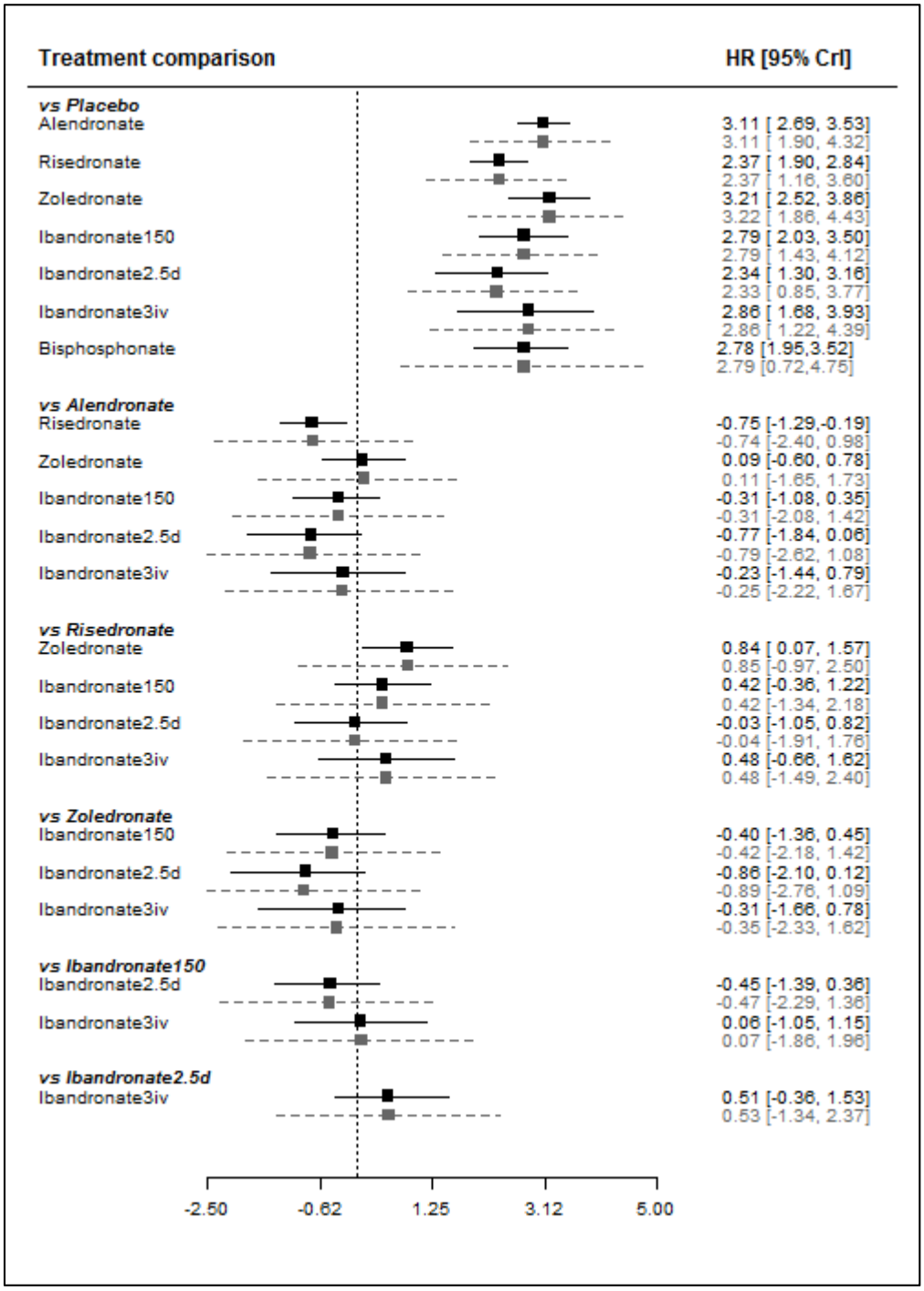
The sample mean ages of the participants in each study ranged from 50.5 to 78.5 years, with overall mean 64.1 years. Figure 64 presents the relationship between mean age of trial participants and treatment effect assuming a common interaction for each treatment. The model fitted the data well with a total residual deviance of 53.97 (compared to 59 data points). The DIC was 97.99 suggesting that the model including age as a covariate did not improved the model fit. The between study standard deviation was estimated to be 0.55 (95% CrI: 0.31, 0.88), and the between treatment standard deviation was estimated to be 0.56 (95% CrI: 0.18, 1.73). The interaction term for study duration in this model was 0.86 (95% CrI: 0.47, 1.25). There was no evidence for an interaction between age and treatment effect, with the interaction term estimated to be 0.01 (95% CrI: -0.04, 0.06). A model in which the treatment effect modifier for age was treated as separate but related (i.e. exchangeable) for each treatment was fitted but this did not improve the model fit, DIC 98.86.

Of the 35 RCTs included in the network, six RCTs included only male participants, 26 female, and three mixed. A meta-regression was conducted to test for different treatment effects according to the proportion of male participants. In line with the licensing indications, interaction terms were not included for ibandronate treatments which are not licenced in men. Figure 65 presents the relationship between proportion of male trial participants and treatment effect, assuming a common interaction for each treatment. The model fitted the data well, with a total residual deviance of 55.98 (compared to 59 data points). The between study standard deviation was estimated to be 0.51 (95% CrI: 0.24, 0.87). The between treatment standard deviation was estimated to be 0.45 (95% CrI: 0.20, 0.79) and the interaction term for study duration in this model was 0.81 (95% CrI: 0.48, 1.14). There was no evidence for an interaction between gender and treatment effect, with the interaction term estimated to be -0.79 (95% CrI: -1.64, 0.14). In fact, including gender did not improve the fit of the model to the data according to a comparison of DICs (98.24 versus 96.5). Exchangeable and related treatment-specific interactions were also considered. The model did not provide a better fit to the data, (DIC 99.30).

The relationship between baseline response and treatment effect was also assessed. For the class effects model with baseline-response adjustment, there was evidence for poor convergence using standard reference priors and so weakly informative priors were used for placebo arms of the RCTs with active treatment. The model fitted the data well, with a total residual deviance of 55.25 and DIC of 99.33. The between study standard deviation was estimated to be 0.51 (95% CrI: 0.49, 0.97) and the between treatment standard deviation was estimated to be 0.50 (95% CrI: 0.19, 1.38).

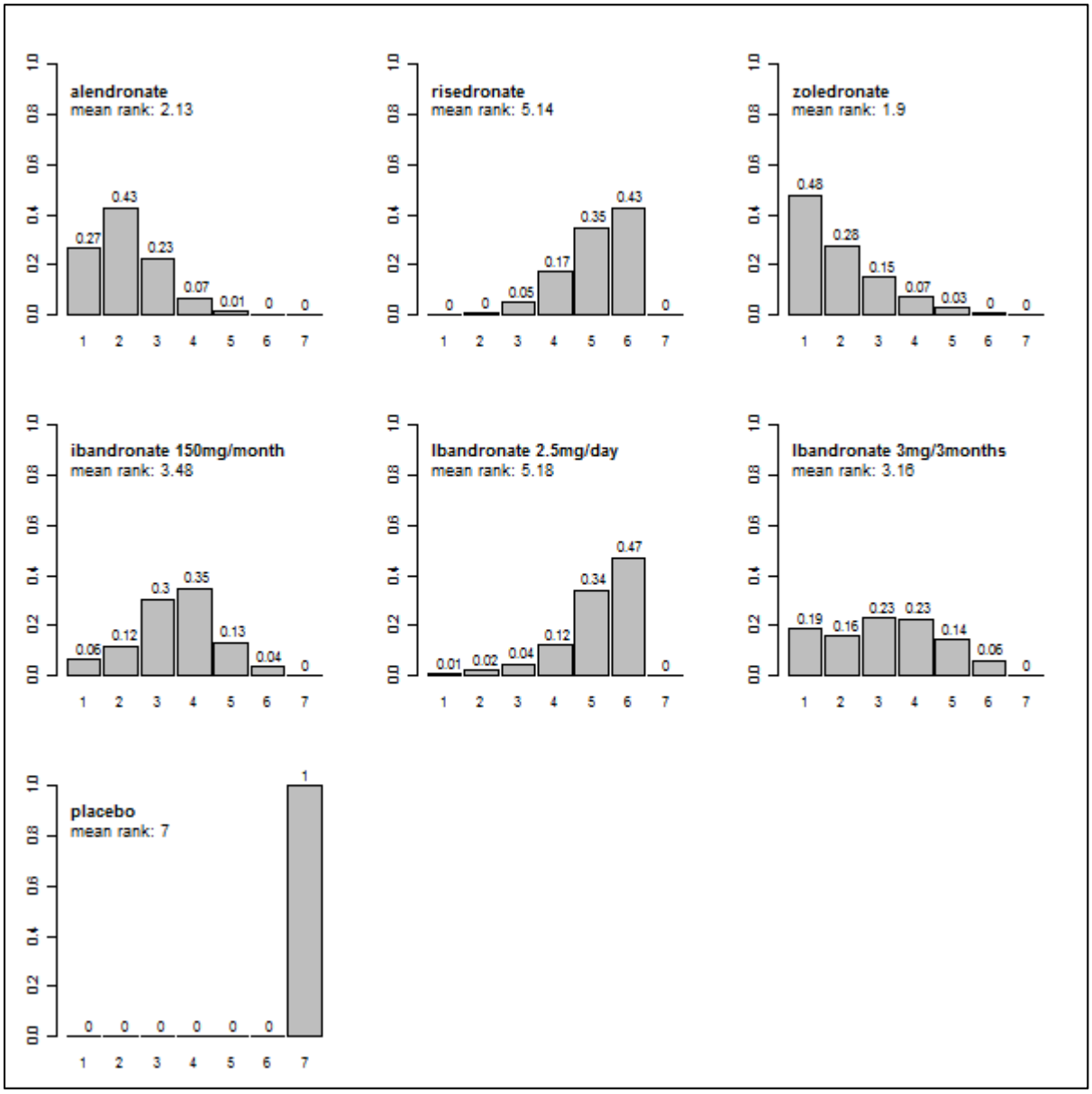
The between study standard deviation from fitting a random effects model to the placebo baseline data was 1.05 (95% CrI: 0.61, 1.78). There was evidence of an interaction between baseline response and treatment effect, with the interaction term estimated to be -0.46 (95% CrI: -0.76, -0.13). Figure 60 presents the relationship between baseline response and treatment effect assuming a common interaction for each treatment. Including baseline response did not improve the fit of the model to the data according to a comparison of DICs, but did reduce the estimate of the between-study standard deviation of the treatment effect. Exchangeable and related treatment-specific interactions were also considered. The model did not provide a better fit to the data (DIC 100.43).

Figure 61: Femoral neck BMD, class effects model. Hazard ratios and 95% credible intervals



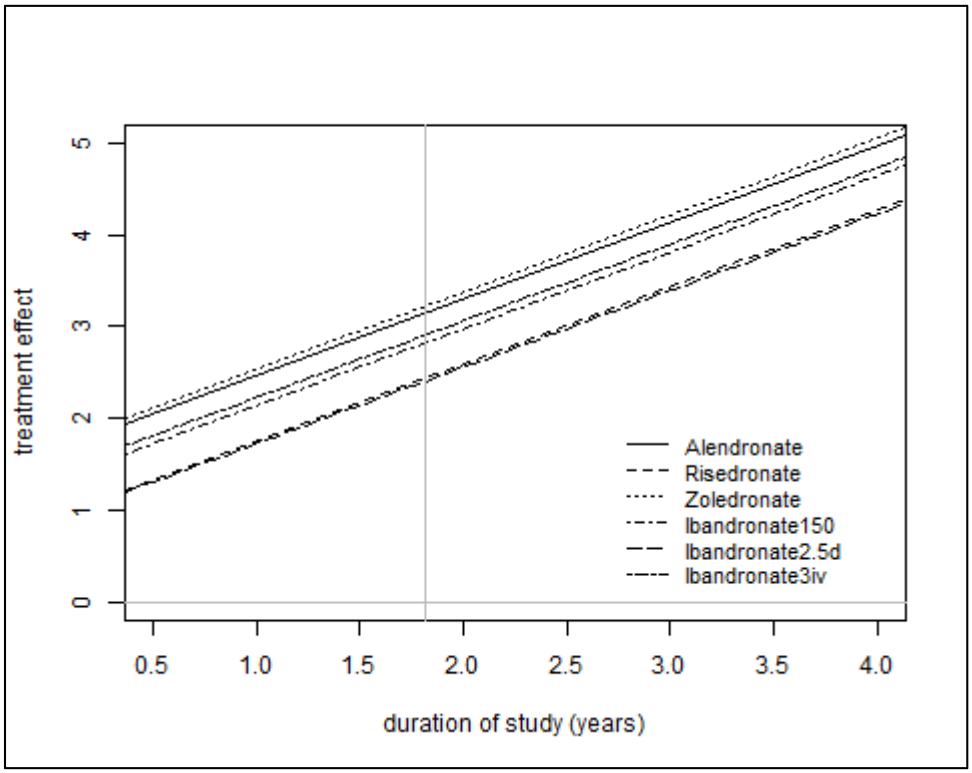
Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the right of the reference line favour the comparator treatment. Treatment effects represent percentage change in BMD for a study of average duration (1.8 years).

Figure 62: Femoral neck BMD, class effects model. Probability of treatment rankings



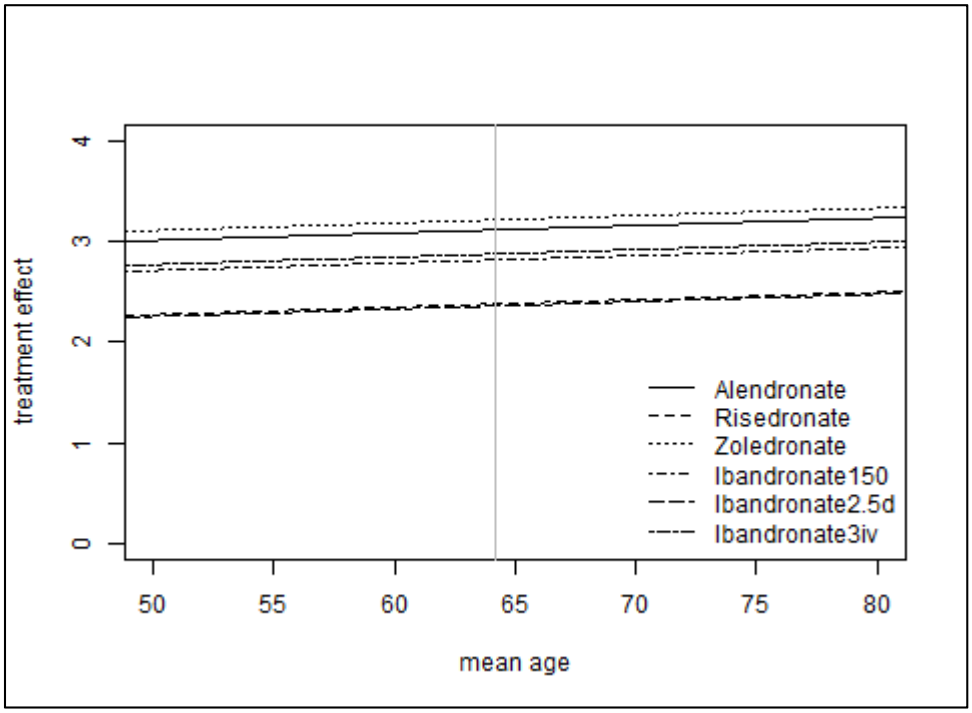
Note: most efficacious =1, least efficacious = 6.

Figure 63: Femoral neck BMD, class effects model. Relationship between treatment effects and duration of study.



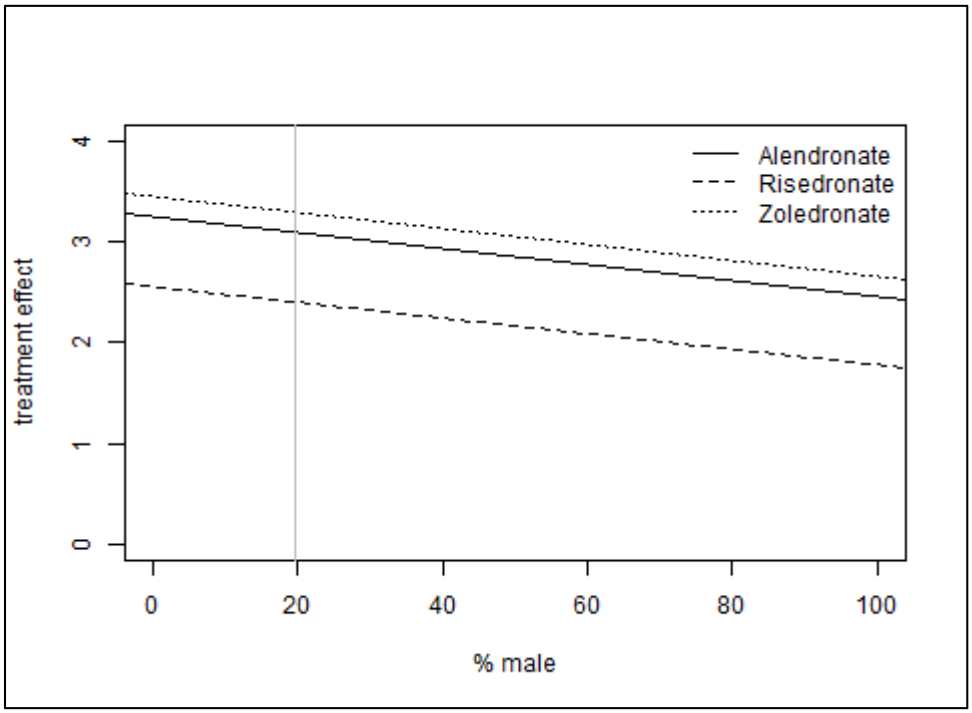
Note: vertical line represents the mean study duration (1.8 years).

Figure 64: Femoral neck BMD, class effects model. Relationship between treatment effects and mean age of trial participants



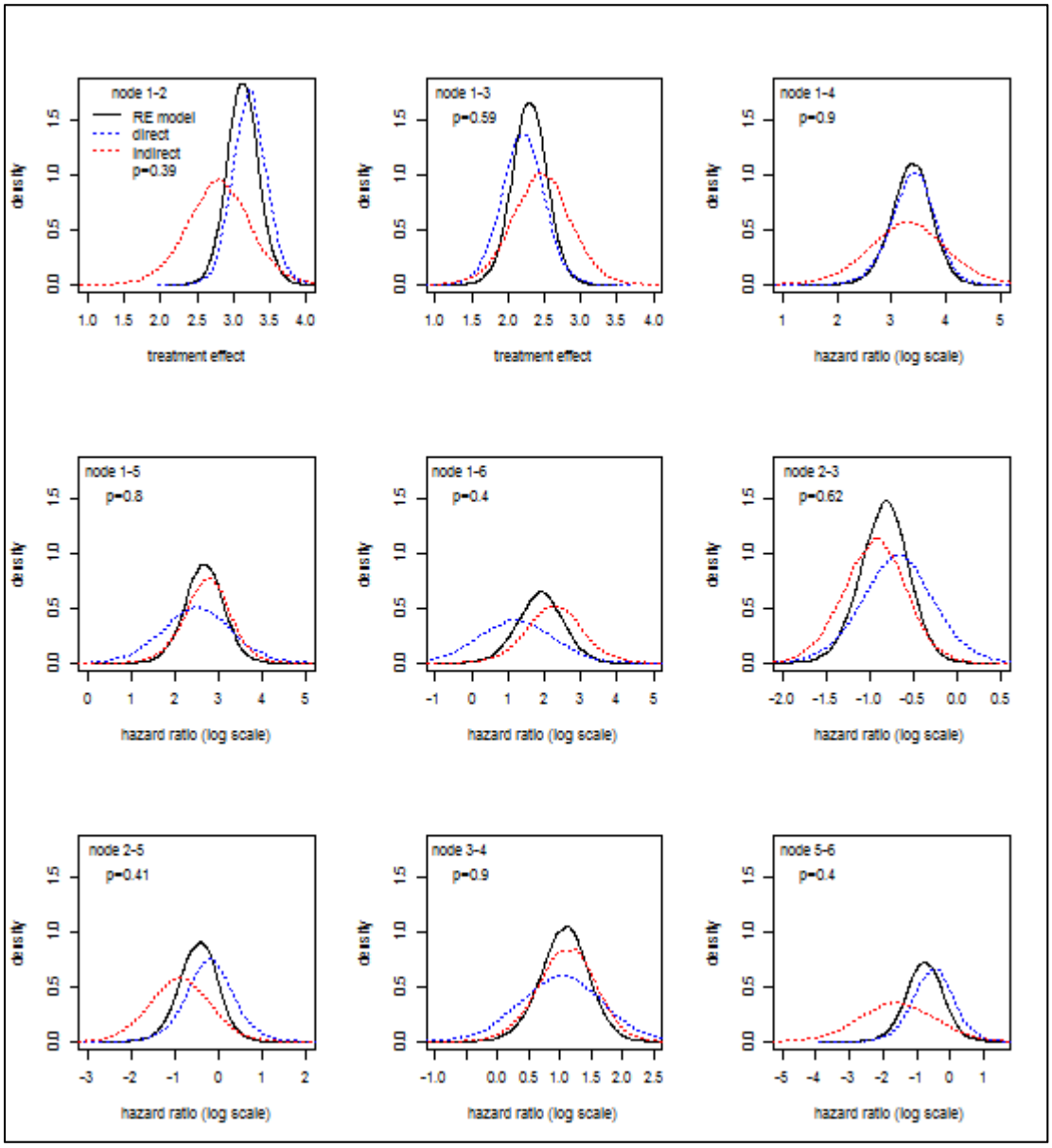
Note: vertical line represents the mean age of trial participants (64.1 years).

Figure 65: Femoral neck BMD, class effects model. Relationship between treatment effects and proportion of male study participants



Note: vertical line represents the average proportion of male trial participants (20%).

Figure 66: Femoral neck BMD, class effects model. Assessing inconsistency using node splitting



Note: comparisons from left to right, top to bottom. node 1-2: placebo-alendronate, node1-3; placebo-risedronate, node 1-4: placebo-zoledronate, node 1-5: placebo-ibandronate 150 mg monthly, node 1-6: placebo-ibandronate 2.5 mg daily, node 2-3: alendronate-risedronate, node 2-5: alendronate-ibandronate 2.5 mg daily, node 3-4: risedronate-zoledronate, node 5-6: ibandronate 150 mg monthly – ibandronate 2.5 mg daily.

5.2.3.5.6 Sensitivity analysis 1

Sensitivity Analysis 1 was conducted by excluding RCTs for which participants were switched from 5 mg per day alendronate to 10 mg per day during the course of the study [57] [66]. This affected the networks for vertebral and non-vertebral outcomes only.

5.2.3.5.6.1. Sensitivity analysis 1- vertebral outcomes, class effects model

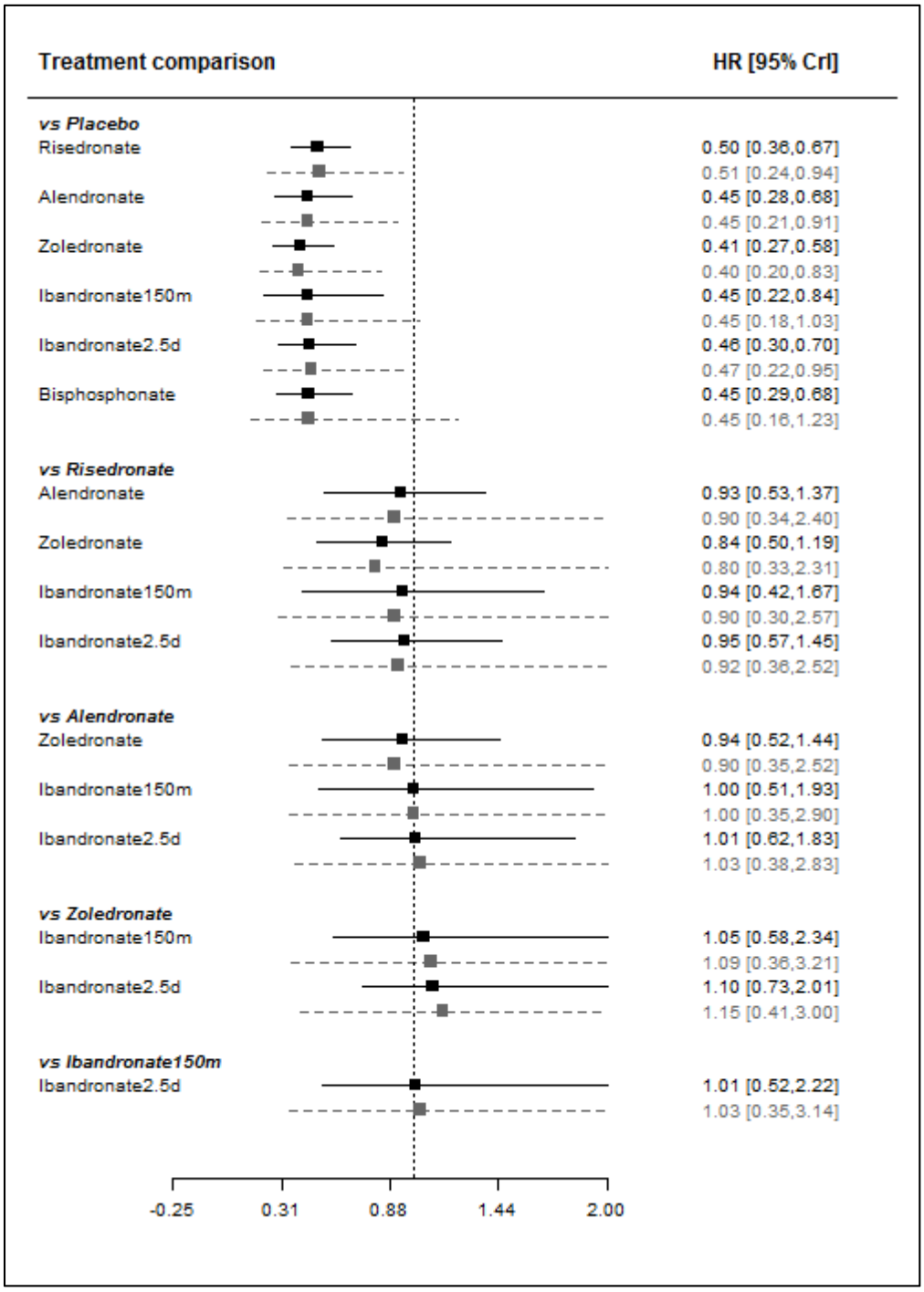
A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate, ibandronate 150 mg monthly and ibandronate 2.5 mg daily relative to placebo on the occurrence of

vertebral fractures. Data were available from 19 RCTs comparing two treatments. The network of evidence is the same as that presented in Figure 42, except for the exclusion of the two alendronate RCTs so that the modified network contains only 4 direct estimates between placebo and alendronate rather than six. Figure 67 presents the effects of each treatment relative to placebo. The model fitted the data well, with a total residual deviance of 36.78 being close to the total number of data points included in the analysis, 38. The between study standard deviation was estimated to be 0.23 (95% CrI: (0.02, 0.59) and the between treatment standard deviation was estimated to be 0.20 (95% CrI: 0.01, 0.96). On exclusion of the two RCTs, a treatment effect of 0.45 (95% CrI: 0.28, 0.68) was estimated for alendronate. The estimated treatment effect was the same as before, but with an increase in uncertainty.

5.2.3.5.6.2. Sensitivity analysis 1, non-vertebral outcomes

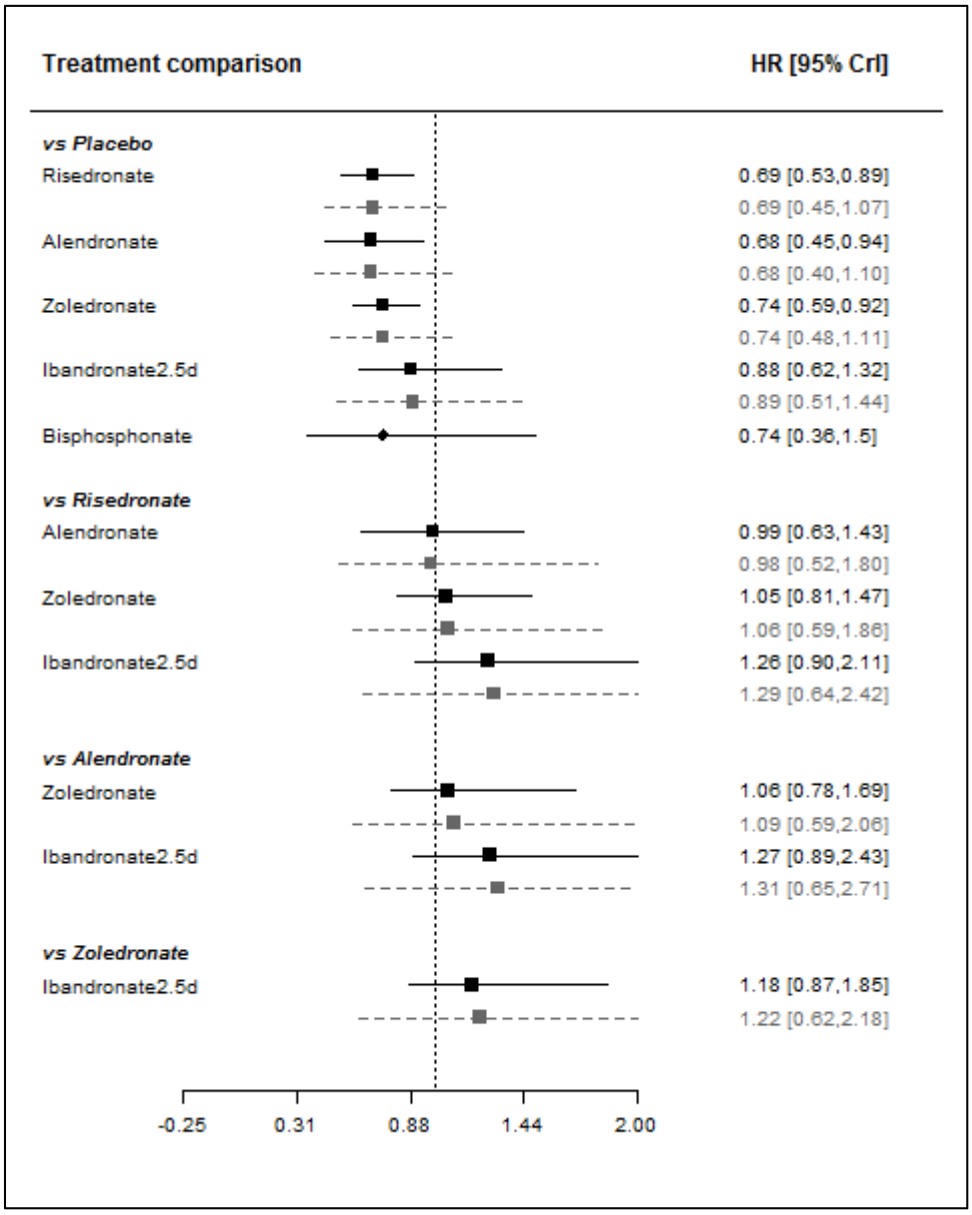
A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate, ibandronate 150 mg monthly and ibandronate 2.5 mg daily relative to placebo on the occurrence of non-vertebral fractures. Data were available from 12 RCTs comparing two treatments. The network of evidence is the same as that presented in Figure 47, except for the exclusion of the two alendronate RCTs so that the modified network contains only three direct estimates between placebo and alendronate rather than five. Figure 68 presents the effects of each treatment relative to placebo. The model fitted the data well, with a total residual deviance of 18.02 being close to the total number of data points included in the analysis, 24. The between study standard deviation was estimated to be 0.10 (95% CrI: 0.00, 0.38) and the between treatment standard deviation was estimated to be 0.23 (95% CrI: 0.01, 1.00). On exclusion of the two RCTs, a more pronounced treatment effect of 0.68 (95% CrI: 0.45, 0.94) is observed for alendronate, compared to a value of 0.80 (95% CrI: 0.65, 0.94) estimated in the main analyses of Section *5.2.3.5.2*, and there is an increase in uncertainty.

Figure 67: Sensitivity 1, vertebral outcomes, class effects model. Hazard ratios and 95% credible interval



Mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Figure 68: Sensitivity 1, non-vertebral outcomes, class effects model. Hazard ratios and 95% credible intervals



Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

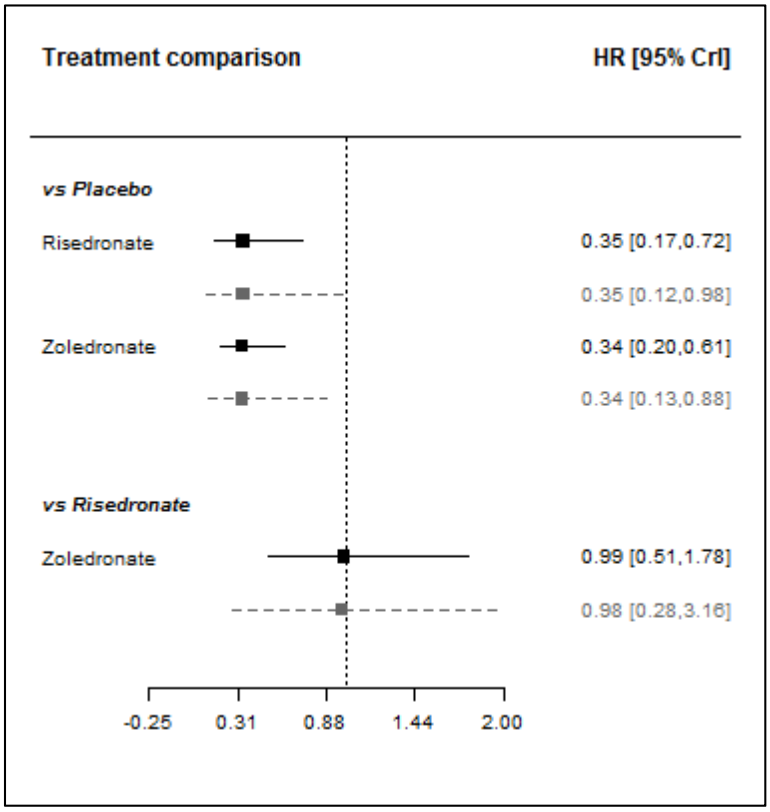
5.2.3.5.7 Sensitivity analysis 2

Sensitivity analysis 2 assessed vertebral fractures, including only the RCTs that used clinical/symptomatic assessment techniques. The network provides two comparisons for placebo against zoledronate and one comparison of placebo against risedronate.

Figure 69 presents the effects of each treatment relative to placebo. The model fitted the data well, with a total residual deviance of 6.32 being close to the 6 data points included in the analysis and DIC of 11.68. The between study standard deviation was estimated to be 0.29 (95% CrI: 0.02, 0.72 and the

between treatment standard deviation was estimated to be 0.18 (95% CrI: 0.01, 0.64). Both treatments are associated with beneficial treatment effects relative to placebo significant at the 5% level. The HR for risedronate is 0.35 (95% CrI: 0.17,0.72), compared to the HR of 0.50 (95% CrI: 0.38,0.67) for all vertebral fractures. For zoledronate, the estimated HR is 0.34 (95% CrI: 0.20,0.61), compared to 0.41 (95% CrI: 0.28,0.56) obtained for all vertebral fracture. No evidence was observed to suggest differential treatment effects according to assessment method.

Figure 69: Sensitivity 2, clinically assessed vertebral outcomes, class effects model. Hazard ratios and 95% credible intervals



5.2.3.5.8 Sensitivity analysis 3

Sensitivity analysis 3 assessed percentage change in femoral neck BMD, excluding the RCTs for which only graphically extracted results were available. A network meta-analysis was used to compare the effects of alendronate, risedronate, zoledronate, ibandronate 2.5 mg daily and ibandronate 150 mg monthly relative to placebo on the percentage change in femoral neck BMD. Data were available from 31 RCTs, each comparing two treatments. Figure 70 presents the network of evidence for femoral neck BMD.

Figure 70: Sensitivity analysis 3. Femoral neck BMD excluding graphically extracted results, network of evidence.

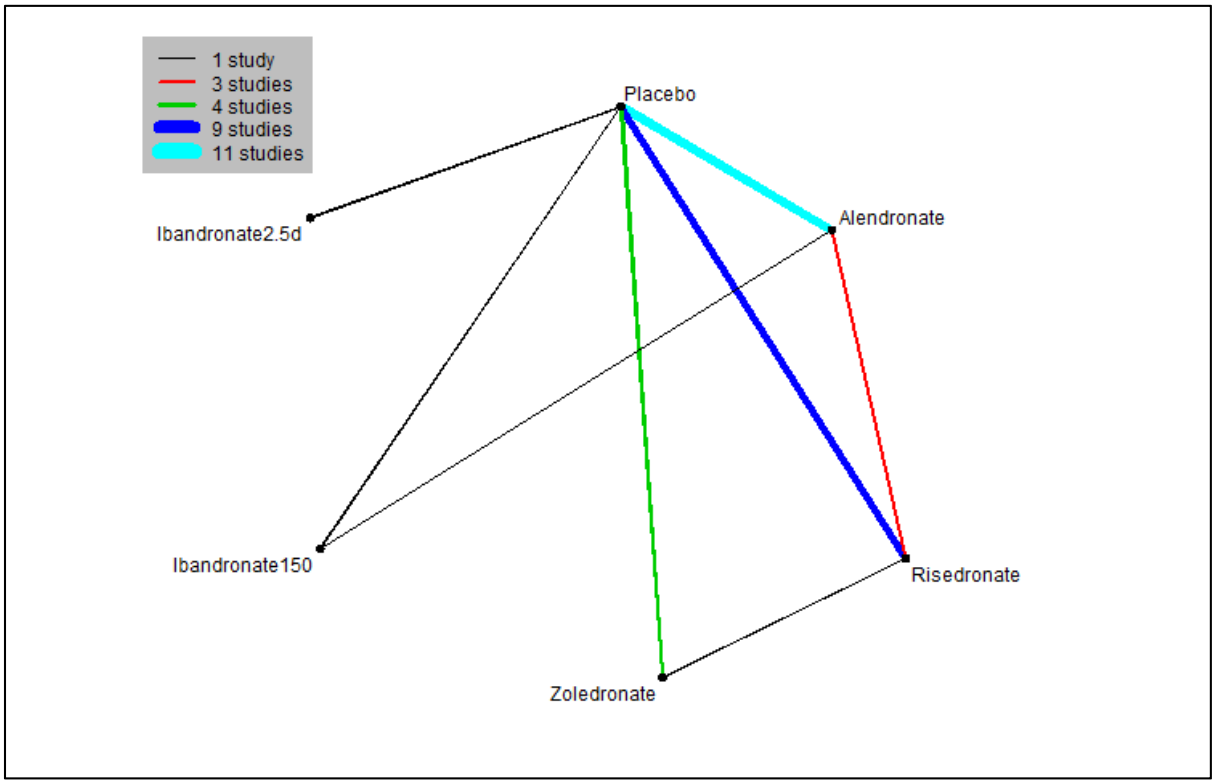
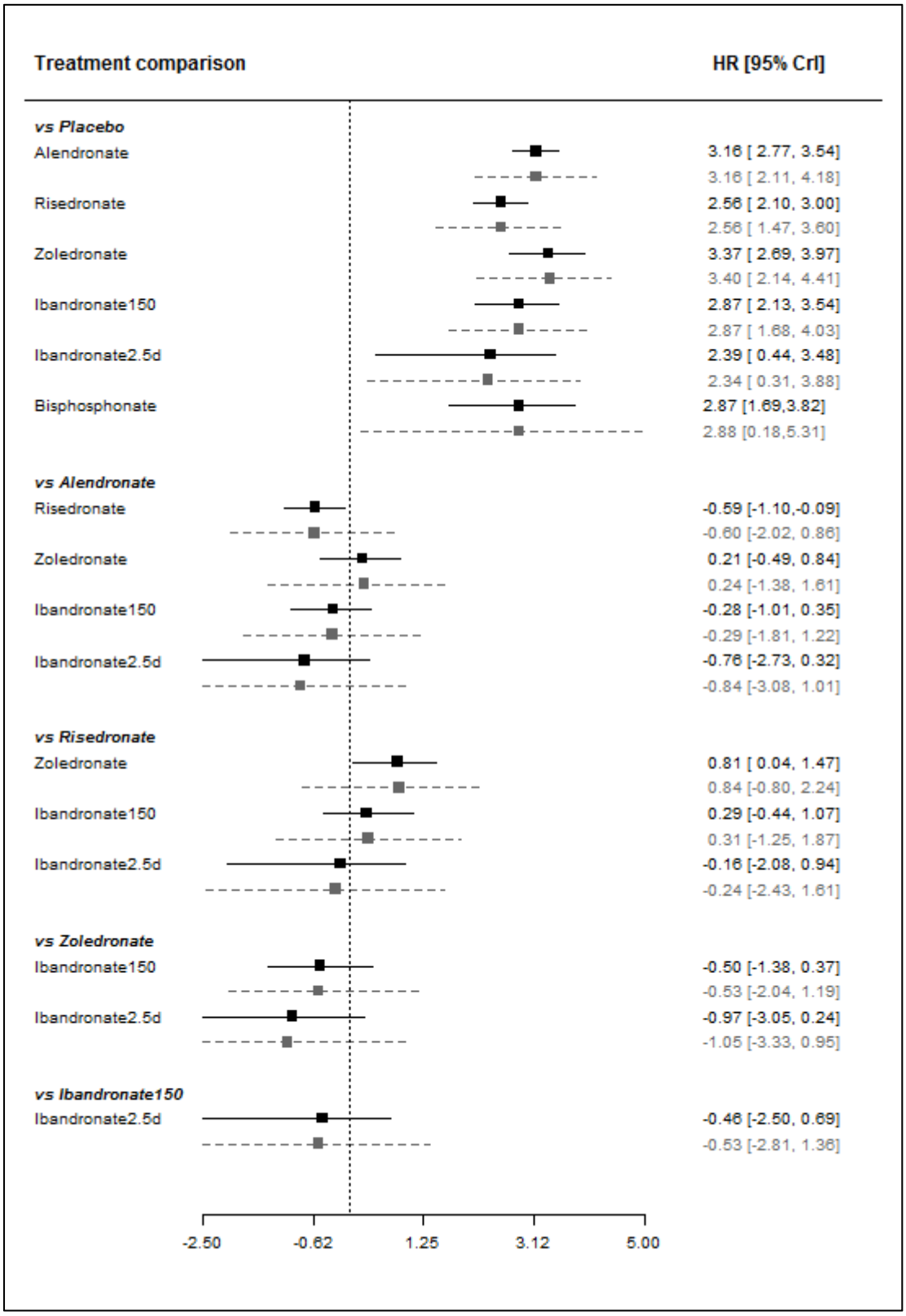


Figure 71 presents the effects of each treatment relative to placebo. The model fitted the data well, with a total residual deviance of 46.41 being close to the number of data points included in the analysis, 55. The DIC was 81.56. The between study standard deviation was estimated to be 0.43 (95% CrI: 0.16, 0.77), implying moderate heterogeneity in treatment effects between RCTs. The between treatment standard deviation was estimated to be 0.65 (95% CrI: 0.15, 2.81). The estimated interaction term for duration of study, assuming a common interaction for each treatment, was 0.86 (95% CrI: 0.55, 1.18).

All treatments were still associated with a beneficial effect relative to placebo, and all treatment effects were statistically significant at a conventional 5% level. As in the full NMA presented in Section *5.2.3.5.5,* zoledronate was associated with the greatest effect, treatment effect 3.37 (95% CrI: 2.69, 3.97).

Figure 71: Sensitivity analysis 3. Femoral neck BMD excluding graphically extracted results, class effects model. Hazard ratios and 95% credible intervals



Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

5.3 Discussion

A total of forty-six RCTs were identified that provided data for the clinical effectiveness systematic review. Alendronate was evaluated against placebo in seventeen RCTs. Daily oral ibandronate was evaluated against placebo in three RCTs and against i.v. administration in one RCT. Daily administration of oral ibandronate was evaluated against monthly administration in one RCT. Risedronate was evaluated against placebo in twelve RCTs, and zoledronate was evaluated against placebo in four RCTs. One RCT evaluated alendronate compared with ibandronate, five RCTs evaluated alendronate compared with risedronate, one RCT evaluated zoledronate compared with alendronate, and one RCT evaluated zoledronate compared with risedronate. Maximum trial duration was 48 months.

The risk of bias associated with the included RCTs was assessed using the Cochrane risk of bias instrument. Attrition ≥10% across treatment groups was evident for 29 (63%) of the included RCTs. Five trials were reported as either open label or single blind and were considered at high risk of bias of performance bias. Blinded outcome assessment was only reported by 13 (29%) trials.

The outcome measures pre-specified in the final NICE scope were addressed by the included trial evidence to varying degrees. Femoral neck BMD was the most widely reported outcome. Fracture was the second most widely reported outcome. Adverse events were reported by the majority of included trials. Across the included trials there was limited reporting on outcomes of compliance (adherence and persistence), hospitalisation and service use; and quality of life.

A total of 27 RCTs provided suitable fracture data for inclusion in the fracture network meta-analysis; nine evaluating alendronate compared with placebo; three evaluating ibandronate against placebo; nine evaluating risedronate against placebo; three evaluating zoledronate compared with placebo, one evaluating alendronate compared with risedronate; and one evaluating zoledronate compared with risedronate. A total of 35 RCTs provided suitable femoral neck BMD data for inclusion in the BMD network meta-analysis: twelve evaluating alendronate compared with placebo; two evaluating ibandronate compared with placebo: one evaluating ibandronate 2.5 mg per day compared with 3 mg i.v. every three months; one evaluating ibandronate 2.5 mg per day compared with 150 mg per month; ten evaluating risedronate compared with placebo; four evaluating zoledronate compared with placebo; two evaluating alendronate compared with risedronate; one evaluating alendronate compared with ibandronate; one evaluating risedronate compared with alendronate; and one evaluating zoledronate compared with risedronate.

Femoral neck BMD may be considered as a surrogate for fracture outcomes. Analysis of the femoral neck BMD data was of interest in order to confirm that the treatment effects were qualitatively the same. The analysis provided no evidence to suggest different treatment effects according to age or gender, with respect to percentage change in femoral neck BMD.

Based on the NMA, all treatments were associated with beneficial effects on each outcome measure relative to placebo. For both vertebral fractures and percentage change in femoral neck BMD the treatment effects were statistically significant at a conventional 5% level for all treatments. Pairwise comparisons between treatments indicated that no active treatments were statistically significantly different to any other active treatment. For vertebral fractures and percentage change in femoral neck BMD, the greatest effect was for zoledronate, though in general the ranking of treatments varied for the different outcomes.

Assessment of vertebral fractures within the studies was based on both clinical and morphometric fractures. Ideally the effect of assessment method would be assessed through meta-regression. However, data for clinical fractures was limited. Consideration of the studies reporting clinical fractures did not provide any evidence to suggest different treatment effects according to assessment method.

The main analyses were based on a class effects model such that the effects of each of the treatments are assumed to be related but not identical. The treatment effects estimated using the class effects model were broadly similar qualitatively (i.e., direction of effect) and quantitatively (i.e., magnitude of effect) to those estimated using the standard random effects model, but with the treatment effects in the class effects model shrunk towards the overall bisphosphonate treatment effect. The qualitative effects of treatment (i.e. direction of effect) were the same for the majority of outcome types and treatments from the class effects and standard random effects models with the exception of zoledronate (hip fractures), ibandronate 150 mg per month (hip and wrist fractures) and ibandronate 2.5mg daily (non-vertebral fractures). Although the point estimates changed from being relative increases in effect in the standard random effects model to relative decreases in effect in the class effects model, there was considerable uncertainty about the true effects as reflected in the credible intervals.

Non-vertebral fractures are used as proxy for fractures of the proximal-humerus, since this latter outcome is not commonly reported. Two studies presented results for proximal humerus fractures, both considering the effects of risedronate against placebo (VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000[87]). A standard random effects meta-analysis of these two studies provided a HR of 0.45 (95% CrI: 0.13, 1.41), which was greater than that estimated for non-vertebral fractures

from the standard random effects network meta-analysis, 0.65 (95% CrI: 0.47, 0.88), and from the class effects network meta-analysis, 0.71 (95% CrI: 0.52, 0.89), but with considerably more uncertainty.

There were no statistically significant differences between treatments in the incidence of upper gastrointestinal events associated with any oral bisphosphonate compared with placebo when data were pooled across RCTs for each bisphosphonate. However, evidence from one RCT indicated a statistically significant risk of upper GI events in men receiving risedronate compared with placebo. Where reported across the RCTs, treatments were prescribed in accordance with the SmPC for oral bisphosphonates to minimise gastric irritation. There was no evidence of significant differences between treatments in mortality across the RCT evidence when data were pooled by bisphosphonate. However, evidence from one RCT indicated a statistically significant greater proportion of men and women dying following hip fracture who were receiving placebo compared with those receiving zoledronate. There was also no evidence of significant differences between treatments in participants withdrawing due to adverse events across the RCT evidence when data were pooled by bisphosphonate. However, evidence from one RCT indicated a statistically significant greater proportion of men receiving alendronate withdrawing due to adverse events compared with placebo.

In agreement with the SmPC there was evidence of influenza-like symptoms associated with zoledronate. There was no statistically significant difference in the incidence of atrial fibrillation associated with zoledronate compared with placebo (one RCT) or risedronate (one RCT). There was no statistically significant difference in the incidence of bone pain associated with zoledronate compared with placebo (one RCT) or alendronate (one RCT). There was evidence of a statistically significant risk of eye inflammation in the first three days following administration of zoledronate compared with placebo (one RCT). Single RCT evidence indicated no statistically significant difference between zoledronate and placebo in the incidence of stroke over 36 months. All RCTs evaluating zoledronate reported no cases of spontaneous osteonecrosis of the jaw in any treatment group during the trial period.

Adverse events of hypocalcaemia and atypical femoral fracture were not reported outcomes by any RCT of any bisphosphonate.

A summary of evidence from systematic reviews that include observational data indicates that alendronate, risedronate and oral ibandronate have similar rates of GI toxicity when compared with placebo. However, prescription event monitoring study data suggests a high level of reporting of a number of conditions in the first month of therapy with alendronate or risedronate, particularly those affecting the upper gastrointestinal tract. Retrospective cohort data also suggests that switching

patients who are stabilized on risedronate to alendronate is associated with an increased risk of GI adverse effects. Zoledronate may be compromised by renal toxicity, and myalgias and arthralgias are evident in the acute phase following i.v. administration. Intravenous bisphosphonates, especially zoledronate, are more likely to predispose patients to osteonecrosis of the jaw. However, in addition to bisphosphonate use, there appear to be several other factors involved in the development of osteonecrosis of the jaw (e.g., dental trauma). There is an increased risk of atypical fracture among bisphosphonate users, however events are rare and long-term bisphosphonate therapy might not be a prerequisite for development of atypical fractures. Moreover, the use of glucocorticoids and proton pump inhibitors are potentially important risk factors for atypical fracture. Bisphosphonates are associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents preclude any definitive conclusions with respect to risk. The review evidence for the use of bisphosphonates and oesophogeal cancer is equivocal.

Evidence for persistence and adherence reported by RCTs was very limited. Where reported, high levels of compliance reported as a pill count were evident over the trial duration. A summary of evidence from systematic reviews including observational data indicates that although patients using weekly bisphosphonate medication follow their prescribed dosing regimens better than those using daily therapy, overall compliance and persistence rates are suboptimal for postmenopausal women receiving bisphosphonate therapy for the treatment of osteoporosis. Furthermore, one third to one half of patients, including men, being treated with bisphosphonates for osteoporosis, do not take their medication as directed.

With the exception of the RCTs evaluating bisphosphonates in steroid users, the majority of RCTs included in the clinical effectiveness systematic review typically excluded people with underlying conditions that affect bone metabolism or people receiving medications that affect bone metabolism. Furthermore, people with history of or receiving medication for upper gastrointestinal tract disorders were also excluded by the majority of included trials. Therefore, the effects of alendronate, ibandronate, risedronate and zoledronate are unknown in these populations.

6. ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Methods

The review of the published evidence surrounding the cost-effectiveness of bisphosphonates in the patient groups eligible for risk assessment within CG146[1] was started by analysing the likely quantity of evidence available. A published systematic review by Muller *et al.,*[153] included cost-effectiveness studies of screen-and-treat strategies for preventing osteoporotic fractures published between January 2006 and November 2011. Of the twenty-four papers included by Muller *et al,* twenty-two examined the cost-effectiveness of bisphosphonates. However, only seven[154-160] of these considered a UK setting. Given the large number of published articles identified from this single systematic review it was decided to limit the review to those papers reporting cost-effectiveness analyses for a UK setting as they would be more applicable to the decision problem defined in Section 2.

6.1.1.1 Identification of studies

A comprehensive search was undertaken to 26 September 2014 to identify papers published in 2006 or later which evaluated the cost-effectiveness of alendronate, risedronate, ibandronate or zoledronate in any of the patient groups eligible for risk assessment within CG146[1]. Subject headings and keywords for 'osteoporosis' were combined with each of the named interventions and an economics search filter. The search strategy is provided in Appendix 2.

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1946 to Present
- Embase (Ovid) 1974 to 2014 September 23
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996-present
- Database of Abstract of Reviews of Effects (Wiley Interscience) 1995-present
- Health Technology Assessment Database (Wiley Interscience) 1995-present
- NHS Economic Evaluation Database (Wiley Interscience) 1995-present
- EconLit (Ovid) 1961 to August 2014
- Cumulative Index to Nursing and Allied Health Literature (EBSCO) 1981 to present
- Science Citation Index Expanded (Web of Science) 1900-present
- Conference Proceedings Citation Index - Science (Web of Science) 1990-present
- BIOSIS (Web of Science) 1926-present

The company submissions were searched to identify any *de novo* economic evaluations described in the company submissions. Published economic evaluations cited within the company submissions were cross-checked with those identified from the search.

6.1.1.2 Inclusions /exclusion criteria

Studies were included in the review if they reported full economic evaluations comparing alendronate, risedronate, ibandronate or zoledronate against each other or against no treatment. Studies were included if any of the population considered would be eligible for risk assessment within CG146. For example studies on post-menopausal women were included whether or not they specified that the women had risk factors as those aged over 65 would be eligible for risk assessment under CG146 even without risk factors being present. Studies which did not assess outcomes using QALYs or report the incremental cost per QALY of alternative treatment strategies were excluded. Studies which did not assess the cost-effectiveness of bisphosphonates within a UK setting were also excluded as discussed above. Studies which assessed the cost-effectiveness of treatment with bisphosphonates at non-licensed doses were also excluded as were studies which used bisphosphonates for other indications such as the treatment of Paget's disease or metastatic bone disease. Studies published prior to 2006 were excluded on the basis that the estimates of cost-effectiveness from older published studies are unlikely to be directly applicable to the decision problem outlined in the scope due to the availability of generic bisphosphonates which has reduced the price of bisphosphonates over recent years. Studies were included only if they were reported as full papers with conference abstracts being excluded from the review as they present insufficient detail to allow for a rigorous assessment of study quality. Studies not reported in English language were also excluded.

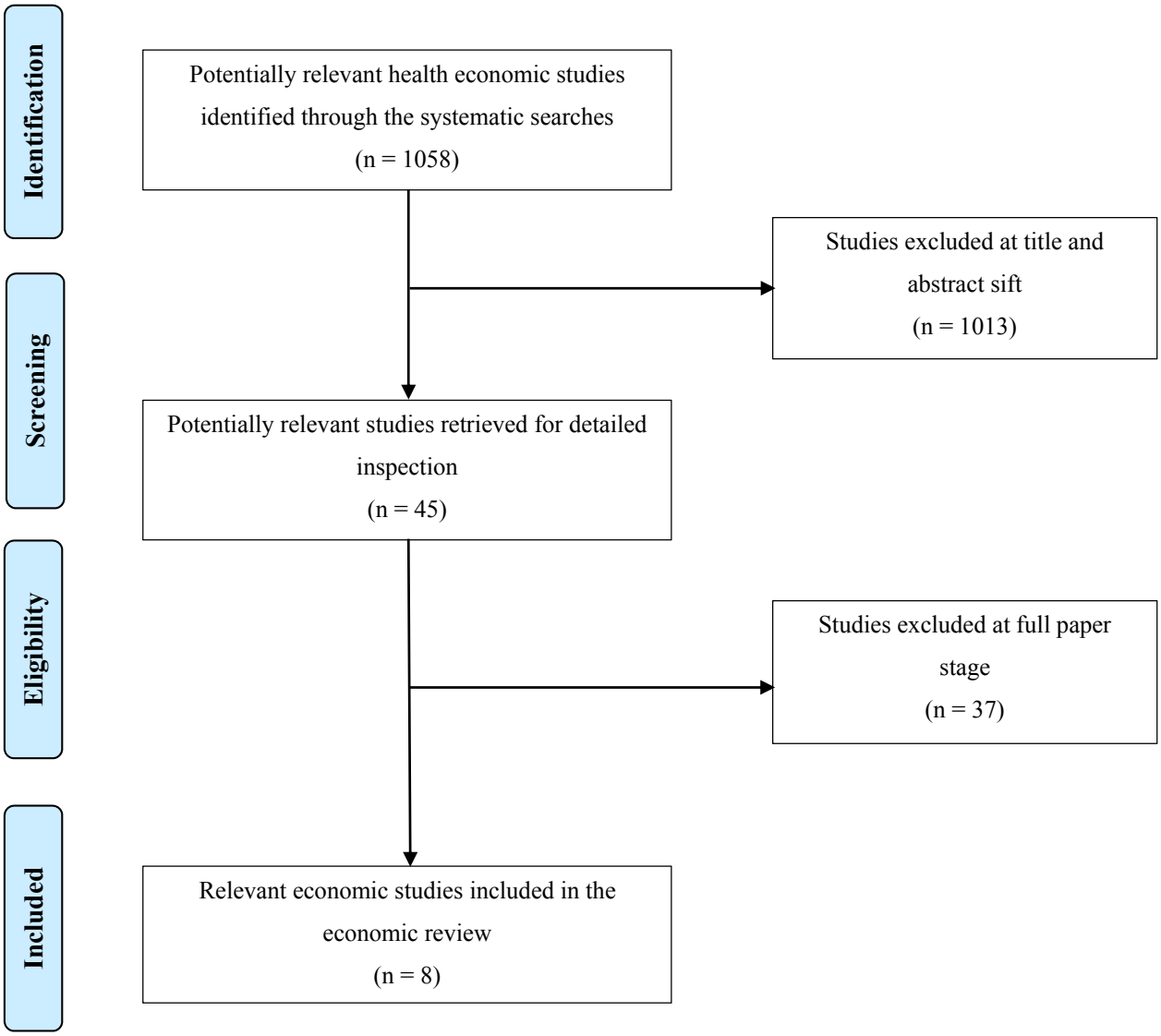
6.1.1.3 Review methods

The results of the economic searches were sifted by title and abstract by one reviewer (AR). The full papers of studies which potentially met the inclusion criteria were retrieved for further inspection. Studies included in the systematic review were examined to determine whether they met the NICE reference case.[161] They were also critically appraised using the checklist published by Phillips *et al.* [162]

6.1.2 Results

The study selection process is summarised in the form of a PRISMA diagram[98] in Figure 72.

Figure 72: Flow diagram of study selection process (adapted from PRISMA) – cost-effectiveness review



6.1.2.1 Quantity of evidence identified

The search identified 1,058 unique articles of which 1,013 were excluded at the title and abstract stage. A further 37 were excluded at the full paper stage with the most common reasons being that they were conference abstracts with limited data presented.

Appendix 8 provides the reasons for exclusion for those papers which were not excluded based on title or abstract. None of the company submissions contained a *de novo* economic evaluation or identified any published analyses not already picked up by through the systematic search.

6.1.2.1 Study characteristics

The characteristics of the included studies are summarised in Table 7. Six of the included studies[154-158,163] were in post-menopausal women with the remaining two being in populations with steroid induced osteoporosis.[159,160]

Three studies[154-156] compared a single bisphosphonate with no treatment, one study[157] compared multiple bisphosphonate strategies head-to-head and against no treatment and four studies[158-160,163] compared a strategy of 'bisphosphonates' against no treatment without specifying the exact bisphosphonate used. All of the included studies assumed that treatment with bisphosphonates lasts five years.

Six studies[154-157,159,163] used a Markov model framework with four[154-156,163] using a cohort-level modelling approach and two[157,159] using a patient-level Markov simulation based on the same underlying model. The remaining two papers[158,160] described an individual patient-based pharmacoeconomic model using patient-level data from two large GP record databases (GPRD and THIN).

Two studies[157,159] explicitly reported using an NHS and PSS perspective while a further three studies[154-156] reported using a healthcare perspective and one reported a societal perspective[163]. The remaining two studies[158,160] did not explicitly report their perspective although many of the costs used were taken from Stevenson *et al.*[157] which used an NHS and PSS perspective. Discounting consistent with the current NICE reference case (3.5% for both costs and QALYs) was applied in four of the studies[154-156,163] whereas alternative discounting at rates (6% for costs and 1.5% for QALYs) were used in the remaining four papers[157-160]. The time horizon varied from six years to a lifetime horizon or age of 100 years.

Table 7: Characteristics of included studies – cost-effectiveness review

First author **Location**	**Population Interventions**	**Type of evaluation**	**Perspective**	**Time Horizon**	**Cost year Cost discount rate**	**Cost source**	**Benefits population Benefits discount rate**	**Benefits source Benefits instrument**	**Effectiveness data**
Van Staa [160] UK	Oral glucocorticoid users age 40+ Five years bisphosphonates vs. no treatment	Individual patient based model	Not reported	Six years	2003/4 6%	Analysis of resource allocation & standard UK reference sources	United Kingdom 1.50%	Observational data EQ-5D	Retrospective survey of medical notes
Kanis [155] UK	Post-menopausal women with risk factors Five years alendronate vs. no treatment	Markov cohort model	Healthcare	Ten years & lifetime	Not reported 3.50%	UK HES data combined with Swedish data	Sweden, Europe & UK 3.50%	Observational data EQ-5D	Recent meta-analysis of trial results
Van Staa[158] UK	Post-menopausal women Five years alendronate/risedronate vs. no treatment	Individual patient based model	Not reported	Ten years	Not reported 6%	Analysis of resource allocation & standard UK reference sources	United Kingdom 1.50%	See Stevenson et al[5] EQ-5D	Retrospective survey of medical notes

First author **Location**	**Population** **Interventions**	**Type of evaluation**	**Perspective**	**Time Horizon**	**Cost year** **Cost discount rate**	**Cost source**	**Benefits population** **Benefits discount rate**	**Benefits source** **Benefits instrument**	**Effectiveness data**
Borgstrom [154] UK	Post-menopausal women Five years risedronate vs. no treatment	Markov cohort model	Healthcare	Patient age 100 years	2006 3.50%	Standard UK & Swedish reference sources	Sweden & UK 3.50%	Observational data EQ-5D	Recent meta-analysis of trial results
Stevenson [157] UK	Post-menopausal women Multiple interventions*	Patient level Markov model	NHS & PSS	Patients lifetime	2001/2 6%	Standard UK reference sources	Not reported 1.50%	Observational data EQ-5D	Meta-analysis conducted by authors
Strom [156] UK	Patients from the fracture intervention trial Five years alendronate vs. no treatment	Markov cohort model	Health payer	Patient age 100 years	2004 3.50%	Standard UK reference sources, academic papers personal communication	Sweden & UK 3.50%	Observational data EQ-5D	Results of the fracture intervention trial
Kanis [159] UK	Oral glucocorticoid users age 40+ Five years bisphosphonates vs. no treatment	Patient level Markov model	NHS & PSS	Ten years and lifetime	2004/5 (Drugs 2006) 6%	Analysis of resource allocation & standard UK reference sources	Sweden 1.50%	Observational data EQ-5D	Meta-analysis conducted by authors

First author **Location**	**Population** **Interventions**	**Type of evaluation**	**Perspective**	**Time Horizon**	**Cost year** **Cost discount rate**	**Cost source**	**Benefits population** **Benefits discount rate**	**Benefits source** **Benefits instrument**	**Effectiveness data**
Borgstrom [163] Australia, Germany, Japan, Spain, Sweden, UK, USA	Post-menopausal women Five years bisphosphonates vs. no treatment	Markov cohort model	Societal	Patient age 100 years	2004 3.50%	Standard UK reference sources & academic papers	Sweden 3.50%	Observational data EQ-5D	Assumption

*No treatment; raloxifene; hormone replacement therapy; calcium; calcium plus vitamin D; calcitonin; alendronate; alfacalcidol; fluoride; pooled bisphosphonate.

6.1.2.2 Evidence sources used

The study conducted by Stevenson *et al.*[157] conducted a systematic review of the literature to estimate the costs associated with osteoporotic fractures. The remaining studies used various sources including personal communication and pre-exiting literature with two studies quoting the same source, Stevenson *et al.*[164]

For all published cost-effectiveness studies the costs of the pharmaceutical agents were ultimately taken from the appropriate version of the British National Formulary for their cost year. The costs of case finding, bone mineral density testing and consultations with general practitioners was obtained from various sources including the appropriate versions of the NHS Reference Costs and the Unit Costs of Health & Social care or assumed.

Health related quality of life was obtained using utility multipliers for fracture states taken from the literature. The studies use different categories of fracture with hip fracture, vertebral fracture, forearm/wrist fracture, humerus fracture being the most common. One study had the additional categories of pelvic fracture, tibia fracture, clavicle, scapula or sternum fracture and rib fracture.[159] Three studies further split hip fracture into hip fracture leading to nursing home admission and hip fracture not leading to nursing home admission.[157,158,160] Seven studies split utility multipliers for fractures into those for the year of fracture and those in subsequent years[154-160].The remaining study split multipliers for fractures into those for the year of fracture and those in the year following fracture and those in subsequent years.[163]

6.1.2.3 NICE reference case

The two studies by van Staa *et al.*[158,160] both used data from a retrospective analysis of patient notes rather than RCT evidence as required by the NICE reference case. They also reported results using a ten year time horizon rather than the lifetime horizon again as required by the NICE reference case. The study by Borgstrom *et al.*[163] failed to meet the requirements of the NICE reference case as the relative risk reduction used in the study was based on an assumption involving the expected distribution of osteoporotic fractures dependent on age and the subsequent utility loss rather than the evidence. Additionally the study by Strom *et al.*[156] failed to meet the requirements of the NICE reference case by using efficacy data from a single RCT, however, it did present the results of a sensitivity analysis using data from a published meta-analysis. Two papers, Stevenson *et al.*[157] and Kanis et al,[159] which used the same underlying model but applied it in two different populations, used differential discount rates of 6% for future costs and 1.5% for future benefits rather than 3.5% for both future costs and future benefits as required by the NICE reference case. However, Kanis *et al.*[159] did report that using discount rates of 3.5% for both future costs and future benefits only had a minor effect on the results. Additionally to the points above none of the included studies compared all four

bisphosphonates specified within the scope of this appraisal in a fully incremental analysis as required by the NICE reference case.

6.1.2.4 Quality of studies

The quality of the studies was generally good when appraised using the checklist published by Phillips *et al.*[162] Responses for each individual study are provided in Table 8. Five of the studies met more than 50% of the checklist criteria.[154-157,159] The studies commonly performed badly on the questions related to internal and external consistency with none of the models providing an adequate description of the quality assurances processes used to demonstrate internal validity and none demonstrating that the model has been calibrated against external data sources. All of the models assessed patient level heterogeneity by running the model for subgroups of patients with different characteristics. However none of the papers adequately address all types of uncertainty (structural, parameter, methodological). Three of the models[159,156,157] assessed parameter uncertainty using analysis (PSA) but in the other four cases this was either not done or not clearly reported. Only two of the studies adequately addressed the quality of the input data and there was limited discussion of the methods used to derive the utility weights applied in the model.

6.1.3 Study conclusions

All of the studies report a range of incremental cost-effectiveness ratios (ICERs) for patients with different characteristics. Patient age, bone mineral density, the presence of prior fracture and the presence of other clinical risk factors all appear to have a significant influence on the ICER based on the included studies. The duration of treatment and the offset duration (the time over which the treatment still has an effect on fracture risk following discontinuation), as well as patient adherence to treatment may have a lesser influence on the cost effectiveness. Given that none of the studies used current prices for bisphosphonates and these have fallen substantially since the time these studies were published, further details on the ICERs are not reported.

Table 8: Quality assessment of the included studies – cost-effectiveness

Criterion	Question	Van Staa[160]	Kanis[155]	Van Staa[158]	Borgstrom[154]	Stevenson[157]	Strom[156]	Kanis[159]	Borgstrom[163]
S1	Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Is the objective of the evaluation and model specified consistent with the stated decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Is the primary decision maker specified?	No	Yes	No	Yes	Yes	No	Yes	No
S2	Is the perspective of the model clearly stated?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
	Are the model inputs consistent with the stated perspective?	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes
	Has the scope of the model been stated and justified?	No	Yes	Yes	Yes	Yes	Yes	Yes	No
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Are the sources of data used to develop the structure of the model specified?	No	Yes	No	Yes	Yes	Yes	Yes	No
	Are the causal relationships described the model structure justified appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S4	Are the structural assumptions transparent and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
S5	Is there a clear definition of the	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Criterion	Question	Van Staa[160]	Kanis[155]	Van Staa[158]	Borgstrom[154]	Stevenson[157]	Strom[156]	Kanis[159]	Borgstrom[163]
	options under evaluation?								
	Have all the feasible and practical options been evaluated?	No	No	No	No	Yes	Yes	Yes	No
	Is there justification for the exclusion of feasible options?	No	No	No	No	N/A	N/A	N/A	No
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S7	Is the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in questions and the impact of interventions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S9	Is the cycle length defined and justified in terms of the natural history of the disease?	N/A	Yes	N/A	Yes	Yes	Yes	Yes	No
D1	Are the data identification methods transparent and appropriate given the objective of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	Where choices have been made between data sources, are these justified appropriately?	No	Yes	No	No	Yes	Yes	Yes	No
	Has particular attention been paid to identifying data for the important parameters in the model?	Yes	No	Yes	Yes	Yes	Yes	Yes	No
	Has the quality of data been assessed appropriately?	No	No	No	No	Yes	No	Yes	No
	Where expert opinion has been	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Criterion	Question	Van Staa[160]	Kanis[155]	Van Staa[158]	Borgstrom[154]	Stevenson[157]	Strom[156]	Kanis[159]	Borgstrom[163]
	used are the methods described and justified?								
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
D2a	Is the choice of baseline data described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	Are transition probabilities calculated appropriately?	N/A	Unknown	N/A	Unknown	Unknown	Unknown	Unknown	Unknown
	Has half-cycle correction been applied appropriately to both costs and outcomes?	N/A	Unknown	N/A	Yes	Unknown	Unknown	Unknown	Unknown
	If not has the omission been justified?	N/A	-	N/A	N/A	-	-	-	-
D2b	If relative treatment effects have been derived from trial data, have they been synthesised correctly using appropriate techniques?	N/A	N/A	N/A	Yes	Yes	Yes	Yes	N/A
	Have the methods and assumptions used to extrapolate short term results to final outcomes been documented and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Have assumptions regarding the continuing effect of treatment once treatment is completed been documented and justified?	No	Yes	Unknown	Yes	Yes	Yes	Yes	Yes
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	Yes	Yes	N/A	Yes	No	Yes	Yes	Yes
D2c	Are the costs incorporate in the	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Criterion	Question	Van Staa[160]	Kanis[155]	Van Staa[158]	Borgstrom[154]	Stevenson[157]	Strom[156]	Kanis[159]	Borgstrom[163]
	model justified?								
	Has the source of all costs been described?	No	No	No	Yes	Yes	Yes	Yes	No
	Have discount rates been described and justified given the target decision maker?	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes
D2d	Are the utilities incorporated into the model appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Is the source of utility weights referenced?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Are the methods of derivation of the utility weights justified?	No	Yes	No	No	Yes	No	Yes	No
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	Yes	No	Yes	Yes	Yes	Yes	No
	Has the use of mutually inconsistent data been justified (i.e. are the assumptions and choices appropriate)?	No	No	No	No	No	No	No	No
	Is the choice of data incorporation transparent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	If data have been incorporated as distributions has the choice of distribution for each parameter been described and justified?	No	Unknown	No	No	No	No	No	No
	If data have been incorporated as distribution, is it clear that second order uncertainty is reflected?	No	Yes	No	Yes	Yes	Yes	Yes	No
D4	Have the four principal types of uncertainty been addressed?	No	No	No	No	No	No	No	No
	If not has the omission of particular forms of uncertainty been justified?	No	No	No	No	No	No	No	No
D4a	Have the methodological uncertainties been addressed by running alternative versions of the	No	No	No	No	No	No	No	No

Criterion	Question	Van Staa[160]	Kanis[155]	Van Staa[158]	Borgstrom[154]	Stevenson[157]	Strom[156]	Kanis[159]	Borgstrom[163]
	model with different methodological //assumptions?								
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	No	No	No	No	Yes	No	Yes
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D4d	Are the methods of assessment of parameter uncertainty appropriate?	No	Unknown	No	Unknown	Yes	Yes	Yes	No
	If data are incorporated in the point estimates are the ranges used for sensitivity analysis stated clearly and justified?	No	No	No	Unknown	No	Unknown	Unknown	No
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	No	No	No	No	No	No	No	No
C2	Are any counterintuitive results from the model explained and justified?	No	No	No	No	No	No	No	No
	If the model has been calibrated against independent data, have any differences been explained and justified?	No	No	No	No	No	No	No	No
	Have the results of the model been compared with those of previous models and any difference in results explained?	No	Yes	Yes	Yes	No	No	No	No

6.2 Independent economic assessment

6.2.1 Methods

6.2.1.1 Model structure

When designing the model structure, we anticipated that an unbiased estimate of the average cost-effectiveness for groups selected according to their level of absolute risk could only be obtained by calculating the mean cost-effectiveness across a population with heterogeneous characteristics. This is because we expected certain characteristics, such as age, which are not uniform across cohorts selected based on absolute risk, to have a non-linear relationship with cost-effectiveness. For example, age was expected to affect both life-expectancy and the probability of a new admission to a residential care setting following fracture both of which would alter the cost and QALY implications of fracture. We therefore decided to use a patient level simulation approach in which the patient characteristics were allowed to vary stochastically in a manner that reflects our beliefs about their distribution within the general population. Having decided to use a patient level simulation approach, we then decided that a discrete event simulation (DES) approach would be more efficient that a patient level state-transition approach. This is because a DES approach only updates the calculation of costs and benefits when a patient experiences an event rather than making calculations for every model cycle. The cohort modelled includes a substantial proportion of low risk patients as not all patients eligible for fracture risk assessment under CG146[1] are at high risk of fracture. In a low risk cohort it would be common for there to be no fracture events experienced during the patient's lifetime. Calculating costs and QALYs every model cycle is much less efficient in low risk populations than in high risk populations where there may be events occurring every few cycles. The main disadvantage of using a DES approach is that the risk factor tools (FRAX and QFracture) which are recommended for assessing fracture risk in CG146[1] provide estimates of the cumulative risk over a defined time frame (10 years for FRAX and 1 to 10 years for QFracture). In order to convert these estimates of absolute cumulative risk to time to event estimates it was necessary to assume some functional form for event free survival and this required some additional data or assumptions regarding the hazard function.

In general within a DES model, the patient's experience as they progress through the model is determined by the events that occur rather than by the health states they occupy. In our model the main clinical events were fracture and death, with fractures at different sites being processed using separate fracture events. The separate fracture events allowed were as follows: hip; wrist; vertebral; and proximal humerus. These are the sites most strongly associated with osteoporosis and these are the fracture sites included by both the QFracture and FRAX risk calculators. Fractures at additional sites (femoral shaft, humeral shaft, pelvis,

scapula, clavicle, sternum, ribs, tibia and fibula) have been incorporated by increasing the incidence of these four event types rather than by adding additional competing events.

The death event was used to process both all-cause mortality and fracture related deaths. If a particular fracture is sampled to be fatal then the time to death is set equal to the time of fracture plus an additional time assumed to be 3 months. At all other times, the time to death is determined by age and gender specific estimates for all-cause mortality from the general population. As the data provided by the lifetables only allow the year of death to be sampled and not the exact time point, we assumed that all deaths occurred exactly 6 months through the year in which death was sampled to occur. All-cause mortality estimates were not adjusted to remove deaths following fracture and therefore the model may have marginally overestimated the total mortality risk.

In a DES no changes are made to the patient's attributes between events. Therefore, dummy events were used to ensure that certain patient attributes were updated at times other than when experiencing a clinical event (death or fracture). For example dummy events were used to recalculate fracture risks at the end of treatment and at the end of the period when treatment effect is assumed to reach zero. The time between these two points is called the fall-off period. If these two events occurred prior to 5 and 10 years respectively then additional dummy events are scheduled for 5 and 10 years to ensure that all patients have their risk updated at these time points. Dummy events were also used to allow the patient's health utility values to be updated 1 year after a fracture event to allow the acute and chronic consequences of fracture to be incorporated separately. Finally a time horizon event was also included to process final patient outcomes for those patients who do not die before reaching the age of 100. The individual's risk of fracture is updated each time a clinical event, or dummy event, occurs. The model incorporates the following structural assumptions:

- the maximum number of hip fractures that can be experienced is limited to 1 per bone with an additional limit of 4 vertebral fractures, 4 rib fractures and 2 pelvic fractures.

- there are no restrictions on the sequence of fractures that can be experienced

- death attributable to fracture occurs 3 months after fracture (see section 6.2.1.10) with other fracture events possible during this period but no mortality from non-fracture related causes

- no further events can be experienced after death

- a fracture event occurring less than one year after a previous event supersedes the dummy event used to update patient attributes 1 year after fracture thus reducing the acute period for the earlier fracture

- nursing home admission can only occur following fracture and therefore patients who are community dwelling at the start of the simulation do not transfer to nursing home care as they age unless this is simulated to occur following a fracture.

Utility in the model is based on a combination of gender, age, fracture history and residential status (community dwelling or institutionalised). Every time an event occurs the patient's utility value is updated and this utility value is used to calculate the QALYs accrued between one event and the next. Furthermore when calculating the QALYs accrued between events an adjustment is made for age-related utility decrements over the intervening years so that the utility value applied does not remain artificially high when the time between events is long. This is done by assuming a linear fall in utility over the intervening years between events. The utility impact for each fracture type is separated into an acute utility multiplier applied in the first year after fracture and a chronic utility multiplier which is applied in all subsequent years. If more than one fracture has occurred then the chronic multiplier for each fracture is applied but no more than one acute utility multiplier is applied at any one time. A utility multiplier is also applied for institutional versus community living. Due to the use of multipliers the absolute utility decrement for each subsequent fracture is smaller and the patient's utility never falls to below zero. Patients who have a prior fracture (as defined by either the FRAX or QFracture risk calculators) at baseline have the chronic utility multiplier for that fracture type applied for rest of their lifetime.

Two types of costs are applied within the model to capture the consequences of fracture. Acute costs which represent the cost of acute care such as hospitalisations are assumed to occur at the time of the event and are applied for both fatal and non-fatal fractures. Chronic costs which are used to represent the on-going costs of care in the months and years after fracture such as nursing home care, or medication costs for chronic pain are accrued gradually over the time period between events. The chronic cost is set to the maximum chronic cost for all fracture events experienced so far with the maximum chronic cost for any individual being the cost for institutionalised patients. Drug costs are applied from the start of the simulation until the end of the treatment period and are assumed to accrue at a constant rate across time.

Death does not incur any additional costs within the model. For patients who suffer a fatal fracture, the full costs of acute care in the year following fracture are still incurred despite the

reduced survival period of 3 months under the assumption that that majority of acute costs are incurred close the time of fracture.

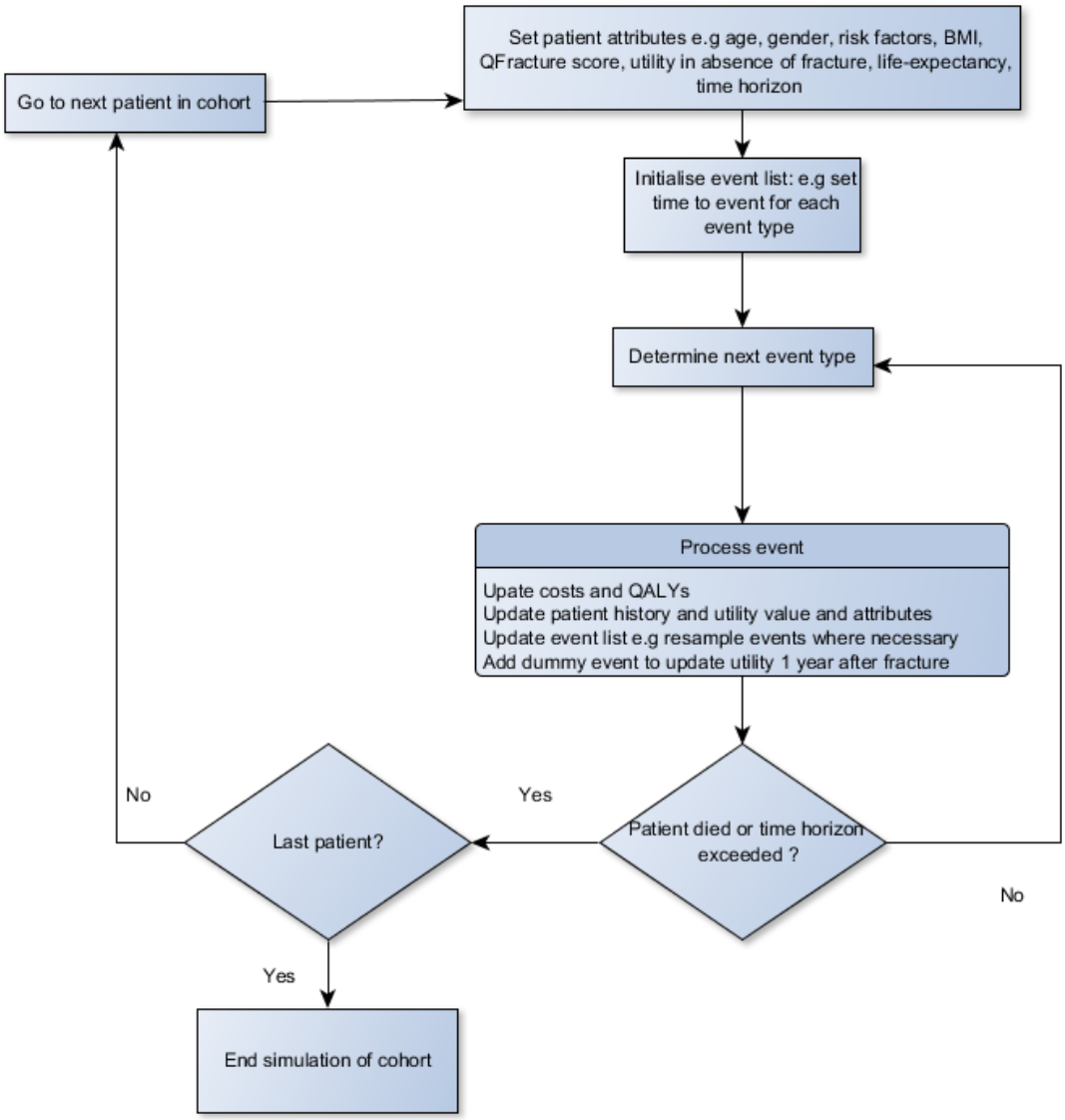
Patients are assumed to stay in the same residential setting (community dwelling or institutional resident) unless they experience a fracture event. So whilst some patients reside in an institutional setting at the start of the simulation, and this proportion is higher in older patients, no patients are simulated to move from the community into an institutional residential setting for reasons other than fracture. This may slightly over estimate the cost savings of preventing fractures as in reality people may enter an institutional residential setting prior to a fracture occurring and therefore will not be at risk of incurring additional costs for residential care following fracture. However this assumption avoids the need for regular events updating the patient's residential status which would reduce the computational efficiency of the DES approach.

The simulation for each individual ends when a fracture related or non-fracture related death occurs or when the time horizon is reached. The time horizon is set according to the patient's starting age so that the simulation ends at age 100 for all patients. This is because the all-cause mortality data is limited to patients aged 100 or less. Costs and benefits have been discounted within the analysis at 3.5% per annum in accordance with NICE reference case.[161]

As CG146 recommends that either FRAX or QFracture is used to estimate the absolute risk of fracture[1], the simulation is run once using each of these tools to estimate fracture risk. First it is run using QFracture to estimate the absolute risk of fracture. During this run the patient characteristics are stored. The model is then re-run using the same set of patients with identical characteristics but with the absolute risk of fracture being defined by FRAX rather than QFracture. This ensures that an identical patient cohort is simulated when using either QFracture or FRAX to estimate the absolute risk of fracture. In the deterministic model, random number control is used to ensure that the random numbers used are identical when running the same patient using both FRAX or QFracture. This eliminates the possibility that results achieved using the different risk calculators are different purely through chance. The same cohort of patients is run for each treatment and for each parameter sample during the probabilistic sensitivity analysis (PSA). This means that the 100th patient has the same characteristics and the same set of random numbers determining their path through the model regardless of the parameter samples selected for the PSA or the treatment being simulated.[161]

The DES model structure is represented in Figure 73.

Figure 73: Schematic of DES model



6.2.1.2 Specifying the model population

In cost-effectiveness analyses that inform NICE Technology Appraisals it is usual for the analysis to address whether particular interventions are cost-effective for the population defined by the licensed indication or for some pre-specified subgroup within the licensed indication. In such cases a model is required which estimates the average cost-effectiveness of the interventions over a pre-specified cohort of patients. However, the economic analyses which informed TA160 and TA161 assessed the costs and benefits of treating patients with varying levels of fracture risk.[20] This was done by considering different combinations of patient characteristics which predict absolute fracture risk. These were age, BMD and the presence or absence of various independent clinical risk factors for fracture, or indicators of low BMD. In the scope for this appraisal[165] it was stated that this MTA would, "develop the

framework to link absolute fracture risk with intervention thresholds, based on cost effectiveness." This implies that the Technology Appraisal Committee would like to know how cost-effectiveness varies with absolute risk rather than the cost-effectiveness of treatment in the licensed population as a whole or within subgroups defined by other factors such as age, BMD or clinical risk factors. Therefore, a *de novo* economic analysis has been designed to estimate the average cost-effectiveness of treating groups of patients who have differing levels of absolute fracture risk.

The NICE guideline on assessing the risk of fragility fracture (CG146) recommends that FRAX[166] or QFracture[167,168] should be used to assess the 10 year absolute risk of fragility fracture. Therefore, our analysis assumes that absolute fracture risk is measured using one of these two tools. (FRAX web version 3.9 and QFracture-2012 open source revision 38 are assumed to be used as these were the versions available online at the time this report was prepared.) In both of these tools absolute fracture risk is dependent on the patient's age, gender, their BMI and the presence or absence of a number of clinical risk factors. In the case of QFracture ethnicity is also taken into account. In the case of FRAX, the patient's BMD can also be incorporated if it is known, but CG146 recommends that BMD is only measured in patients whose absolute fracture risk falls close to a treatment threshold. Therefore our model assumes that BMD is not known as treatment thresholds must be defined for those without a BMD measurement for the recommendations in CG146 to be implemented. The FRAX tool estimates the individual's 10 year absolute risk of hip fracture and their 10 year absolute risk of major osteoporotic fracture (clinical spine, hip, forearm and humerus fracture). The QFracture tool provides the absolute risk of hip and the absolute risk of major osteoporotic fracture (hip, spine, wrist or shoulder), but with the option to vary the timeframe from 1 year to 18 years (the web tool is limited to 10 years). Table 9 summarises the risk factors used by the FRAX and QFracture tools.

Table 9: Summary of risk factors included in FRAX (web v3.9) and QFracture (2012) tools

Patient characteristic	**FRAX[166]**		**QFracture[167,168]**	
	Y/N	Notes	Y/N	Notes
Age	Y		Y	
Gender	Y		Y	
BMI	Y		Y	
BMD	Y	(Optional) T-Score or femoral neck BMD in g/cm^2	N	
Ethnicity	N		Y	Categories are White or not stated, Indian, Pakistani, Bangladeshi, Other Asian, Black Caribbean, Black African, Chinese, other
Previous fracture	Y	Fragility fracture at any site in adult life	Y	Hip, wrist, spine or shoulder
Parental history of fracture	Y	Hip fracture in mother or father	Y	Hip fracture or osteoporosis in parent
Alcohol use	Y	3 or more units daily	Y	Categorised as daily units of <1, 1-2, 3-6, 7-9, >9
Smoking status	Y	Current smoking	Y	Categorised as none smoker, ex-smoker, light (<10 per day) , moderate (10-19 per day) and heavy (>20 per day)
Steroid use	Y	Currently exposed to oral glucocorticoids or past exposure >3 months at dose equivalent to 5mg of prednisolone daily	Y	Taking steroid tablets regularly

Patient characteristic	FRAX[166]		QFracture[167,168]	
Rheumatoid arthritis or systemic lupus erythematosis	Y	Rheumatoid arthritis only	Y	
Secondary osteoporosis	Y	Any disorder strongly associated with osteoporosis. Examples given are type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease	N	Several causes of secondary osteoporosis are included as separate risk factors (see below)
Diabetes	N	Type 1 included under secondary osteoporosis	Y	Type 1 and type 2 specified separately
Living in nursing or care home	N		Y	
History of falls	N		Y	
Dementia	N		Y	
Cancer	N		Y	
Asthma or COPD	N		Y	
Heart attack, angina, stroke or TIA (CVD)	N		Y	
Chronic liver disease	N	Included under secondary osteoporosis	Y	
Chronic kidney disease	N		Y	
Parkinson's disease	N		Y	
Malabsorption	N	Included under secondary osteoporosis	Y	e.g. Crohn's disease, ulcerative colitis, celiac disease, steatorrhea, or blind loop syndrome

Patient characteristic	FRAX[166]		QFracture[167,168]	
Endocrine problems	N	Long standing hyperthyroidism included under secondary osteoporosis	Y	e.g. thyrotoxocosis, hyperparathyroidism, Cushing's syndrome
Epilepsy or taking anticonvulsants	N		Y	
Taking antidepressants	N		Y	
Taking oestrogen only HRT	N		Y	

COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack; CVD, cardiovascular disease; HRT, hormone replacement therapy

A particular level of absolute fracture risk, as measured by FRAX or QFracture, can be achieved in different ways by different individuals. For example, a young patient with many clinical risk factors may have the same absolute risk of fracture as an older patient who has no clinical risk factors. Whilst the absolute risk of fracture is likely to be an important determinant of the cost-effectiveness of treatment with bisphosphonates, other factors may affect cost-effectiveness independently of absolute fracture risk. For example, the cost and QALY consequences of fracture may be more severe in older patients who may be more likely to die or be admitted to a nursing home following fracture. Therefore in a group of patients who have been selected to have the same absolute fracture risk there may be variation in the cost-effectiveness of treatment. If there is a linear relationship between patient characteristics and cost-effectiveness then it is possible to estimate the average cost-effectiveness by calculating the cost-effectiveness for a patient with average characteristics. However, previous work in this area suggests that cost-effectiveness may be non-linearly associated with patient characteristics, such as age.[169] In such cases, an unbiased estimate of the mean cost-effectiveness can be achieved by simulating a patient population with heterogeneous patient characteristics and estimating the average cost-effectiveness across that population.[170]

In this analysis we have simulated a heterogeneous patient cohort that is representative of all patients eligible for risk factor assessment within CG146. We have limited the population to patients aged over 30 years as neither the FRAX nor the QFracture tool has been validated in patients aged under 30. Initially a population of patients aged over 30 is simulated but only those eligible for risk factor assessment with CG146 are included within the cohort used

within the cost-effectiveness analysis. For example, simulated patients without clinical risk factors (any included in QFracture or FRAX) are excluded from the analysis if they are female and aged under 65 or male and aged under 75 and simulated patients are also excluded if they are aged under 50 and do not have either a prior history of fragility fracture or current steroid use. This approach of sampling the whole population and then excluding those not recommended for risk factor assessment by CG146 was necessary as data were not available on the distribution of clinical risk factors within the specific population eligible for risk assessment under CG146.

Once the cohort eligible for risk factor assessment has been defined from within the general population, we have estimated FRAX and QFracture scores for each individual, (where 'score' refers to the absolute risk of fracture over 10 years for the four main fracture sites: hip; wrist; vertebra; proximal humerus). Lifetime costs and QALYs for each patient are then estimated using the cost-effectiveness model. This step is repeated once for no treatment and once for each bisphosphonate treatment strategy. We have then stratified the patients into ten risk categories based on their absolute fracture risk and estimated the average cost-effectiveness of each bisphosphonate compared with no treatment within each risk score category. The cut-offs for each risk category have been set using deciles to ensure that a sufficient number of patients fall into each category to allow the cost-effectiveness to be estimated accurately. The stratification into risk categories is done independently for QFracture and FRAX. As there is not necessarily agreement between the risk scores calculated by these two different risk assessment tools at the patient level, the same patients may not end up in the same risk category when using different tools to define absolute risks.

In order to stochastically sample patient characteristics we needed data on the prevalence of each clinical risk factor and the distribution of continuous factors such as age and BMI. As well as considering the prevalence of individual risk factors it is also important to determine whether there are correlations between any of the patient characteristics so that the sampling process can allow for the fact that some risk factors may be more likely to occur in the same patient than in separate patients. It is difficult to fully characterise the correlation structure of all of the risk factors which go into both the QFracture and FRAX tools without access to a database containing information on all or the risk factors in a large sample of patients. However, it is most important to capture the correlations between those characteristics which are likely to be significant determinants of cost-effectiveness independently of their impact on absolute fracture risk. This is because the prevalence of these factors will determine the distribution of cost-effectiveness within groups who have the same absolute fracture risk.

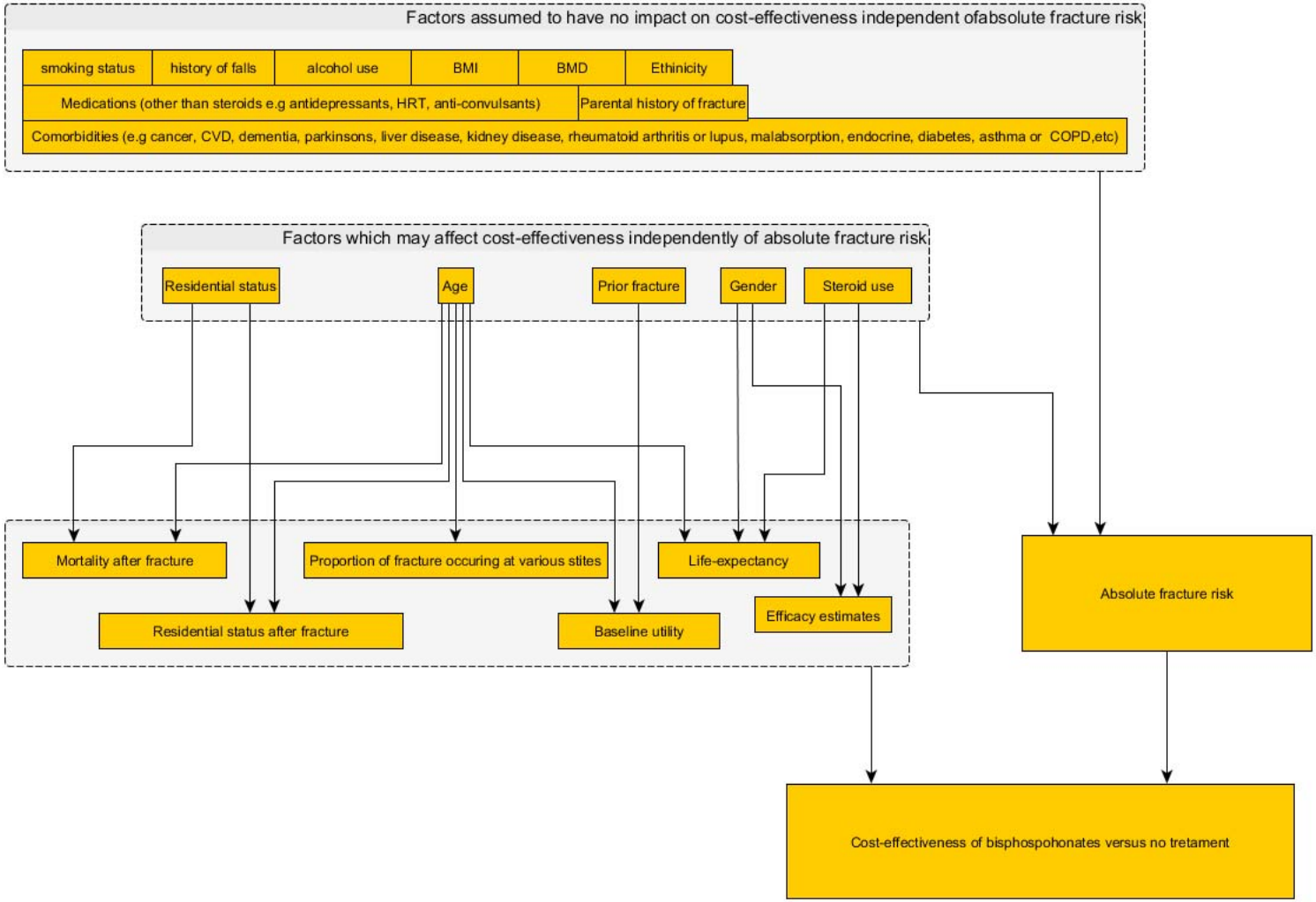
We developed a conceptual model outlining which risk factors are likely to significantly impact cost-effectiveness independently of their impact on absolute fracture risk. This was based on the relationships assumed in published models in this area, advice from our clinical advisors and rapid literature searches. A summary of this conceptual model is shown in Figure 74. Age, gender, prior fracture, steroid use and residential status were identified as risk factors thought to affect cost-effectiveness independently of absolute fracture risk. Further details on the rationale for selecting these risk factors are given in Table 10. Ethnicity, family history of fracture and BMD were excluded as these are expected to affect cost-effectiveness solely through their impact on absolute fracture risk. Whilst some of the remaining risk factors included in either FRAX or QFracture (e.g. alcohol use, smoking status, comorbidities, secondary causes of osteoporosis, medications, BMI, history of falls), might be expected to affect an individual's baseline utility, life-expectancy or their likelihood of living in an institutional residential setting, these relationships were felt to be too weak to include within the model without adding unnecessary complexity to the model structure. Furthermore, many of these conditions are likely to be more prevalent within older patients or those living in residential care and therefore their impact on utility, all-cause mortality or outcomes following fracture may already be captured by the relationship between these variables and age or residential status. We have therefore focused on trying to capture the correlations between age, gender, steroid use, prior fracture and residential status. This has been achieved by looking for age and gender specific estimates of steroid use, prior fracture and residential status as these were considered to be where the most significant correlations would lie. The conceptual model was developed to allow for the possibility that different efficacy data may be applied for different genders and for steroid and non-steroid induced osteoporosis but in the final analysis efficacy evidence was pooled across all included trials reporting fracture outcomes. The potential for increased all-cause mortality in steroid users was noted at the conceptual modelling stage but no difference in life-expectancy was applied in the final model.

Table 10: Patient characteristics that we would expect to affect cost-effectiveness independently of absolute fracture risk

Patient characteristic	Rationale
Age	Age is predictive of the following factors which affect cost-effectiveness independently of absolute fracture risk: • life-expectancy[171] • utility[172] • proportion of fractures occurring at various sites[173] • mortality after hip fracture[174] • residential status after hip fracture[175]
Steroid use	Efficacy data for steroid induced osteoporosis may differ from non-steroid induced osteoporosis (see note below)* All-cause mortality may be higher in steroid users which will affect cost-effectiveness independently of absolute fracture risk
Gender	Efficacy data for males and females may differ (see note below)* Gender is predictive of the following factors which affect cost-effectiveness independently of absolute fracture risk: • life-expectancy[171] • proportion of fractures occurring at various sites[173] • mortality after hip fracture [174] • residential status after hip fracture[175]
Prior fracture	Utility at baseline may be lower in those with significant prior fractures e.g. hip fracture
Residential status	Residential status is predictive of the following factors which affect cost-effectiveness independently of absolute fracture risk: • Utility at baseline • mortality after hip fracture[174] • cost of additional social care following fracture (these will be higher in community dwelling patients who move to an institutional residential setting following fracture than in those already living in an institutional residential setting)

*The conceptual model allowed for this possibility but after considering the efficacy evidence it was decided that data would be pooled across genders and steroid and non-steroid users.

Figure 74: Relationships assumed between individual risk factors and cost-effectiveness



The primary data source used to characterise the patient population was the cohort used to derive the 2012 QFracture algorithm. This study used a large (N=3,142,673) prospective cohort aged 30 to 100 years drawn from a large, validated primary care electronic database. [167] This study was chosen as the primary source of data on patient characteristics as it was considered to be representative of the general UK population and provided data on all of the risk factors included within the QFracture algorithm. For the majority of the clinical risk factors, we used the prevalence within the 2012 QFracture cohort and applied the same prevalence across all ages and across both genders. These risk factors are listed in Table 11 along with the prevalence reported for the 2012 QFracture cohort. Although many of these risk factors are expected to have varying prevalence across different genders and age groups, it was not considered necessary to capture their correlation with age or gender as they are assumed to influence cost-effectiveness only through their impact on absolute fracture risk.

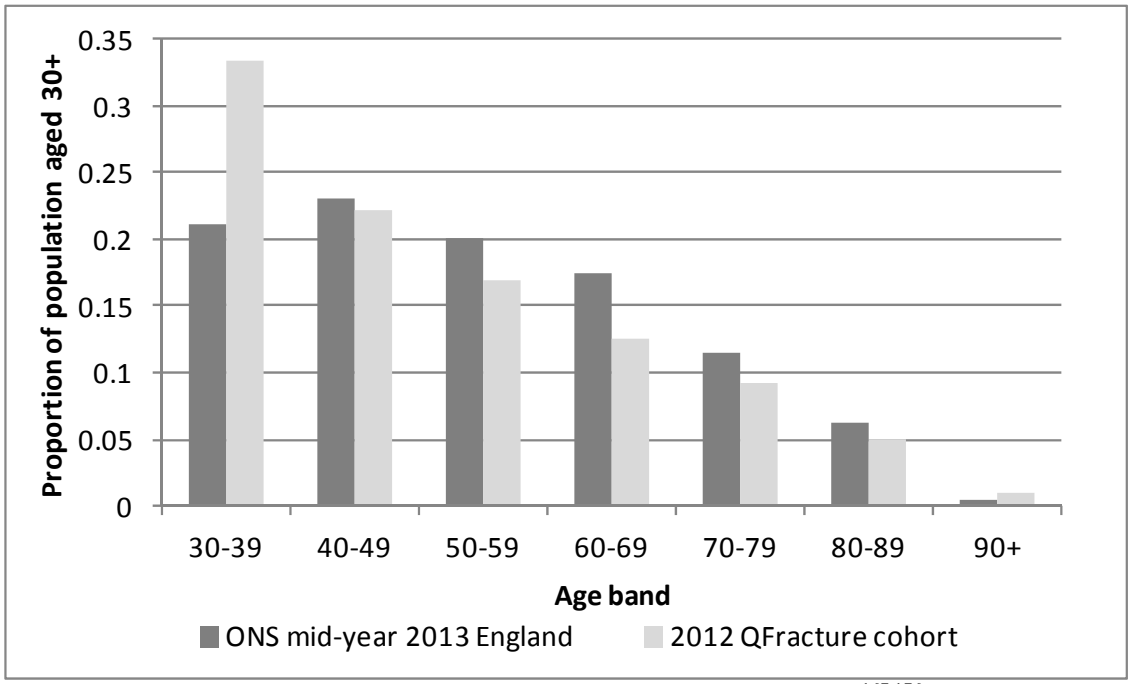
Table 11: Clinical risk factors which were assumed to have a constant prevalence across the cohort.

Clinical risk factors	**Prevalence in 2012 QFracture cohort*** [167]
Dementia	0.6%
History of falls	1.2%
Malabsorption	0.5%
Endocrine disorders	0.5%
Asthma or chronic obstructive airways disease	7.6%
Any cancer	1.9%
Cardiovascular disease	5.3%
Epilepsy diagnosis or prescribed anticonvulsants	1.8%
Chronic liver disease	0.2%
Parkinson's disease	0.2%
Rheumatoid arthritis or systemic lupus erythematosus	0.7%
Chronic renal disease	0.2%
Type 1 diabetes	0.3%
Type 2 diabetes	2.8%
Parental history of osteoporosis	0.3%
Unopposed hormone replacement therapy	2.2% (in the female only subgroup)
Any antidepressant	7.7%

* Prevalence for the derivation cohort is reported here and used in the model but similar values were obtained for the validation cohort.

Whilst data were available on the age distribution for patients within the 2012 QFracture cohort, these data were not provided separately for males and females and the age profile of the UK population is known to differ slightly by gender.[176] Therefore gender specific 2013 mid-year population estimates for England from the office of national statistics (ONS) were used to provide an empirical distribution for patient age.[176] Figure 75 shows how the proportion falling within each band compares between the ONS data and the 2012 QFracture cohort. The data appear to be reasonably well matched except that the QFracture cohort appears to have a lower proportion in the 30-39 year category. The ONS data was considered to be more representative of the population in England and therefore the age of each individual patient was sampled using the gender specific ONS data.

Figure 75: The proportion of those aged 30+ who fall within each age category

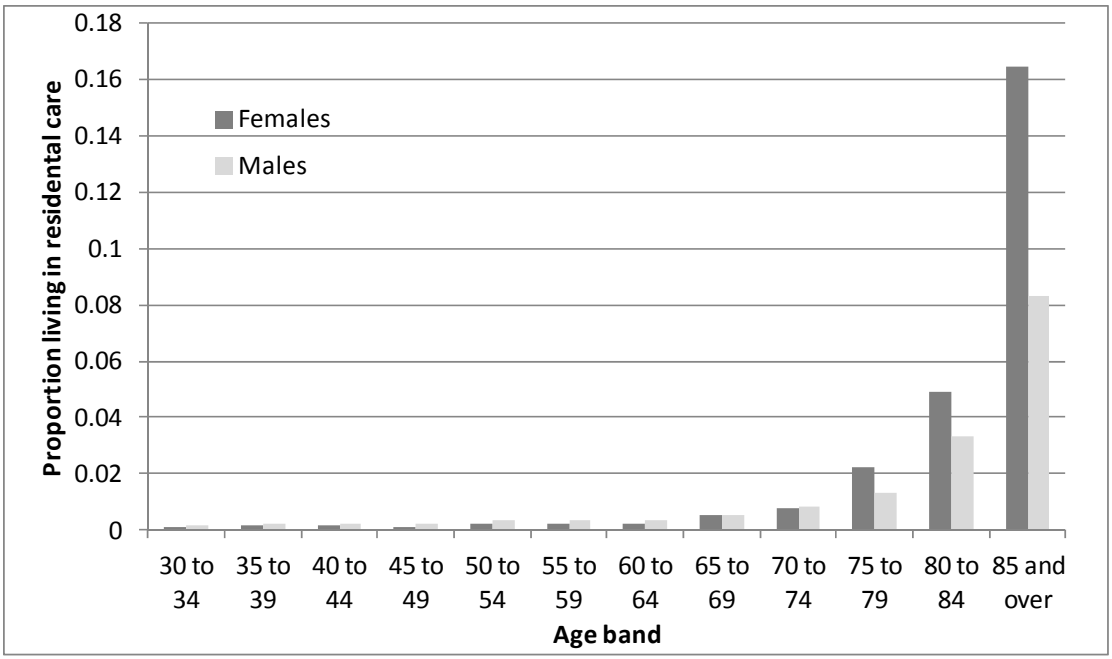


Based on ONS data and the age distribution in the 2012 QFracture cohort[167,176]

The proportion living in an institutional residential setting was estimated from the 2011 census data. Gender specific data were available for 5 year age bands for all people who are usual residents in communal establishments.[177] However, these 5 year estimates included people resident in other types of communal establishments such as children's homes and prisons. Data were also available on specific types of establishments for 10 year age bands.[178] We selected data for people resident in medical and care establishments which included NHS, local authority and other establishments both with and without nursing care. We then used the 5 year data on all communal establishments to divide up the 10 year data into 5 year age

bands. These data, shown in Figure 76 were used to sample whether an individual was living in an institution according to their age and gender.

Figure 76: Proportion living in an institutional residential setting by age band (2011 Census data)

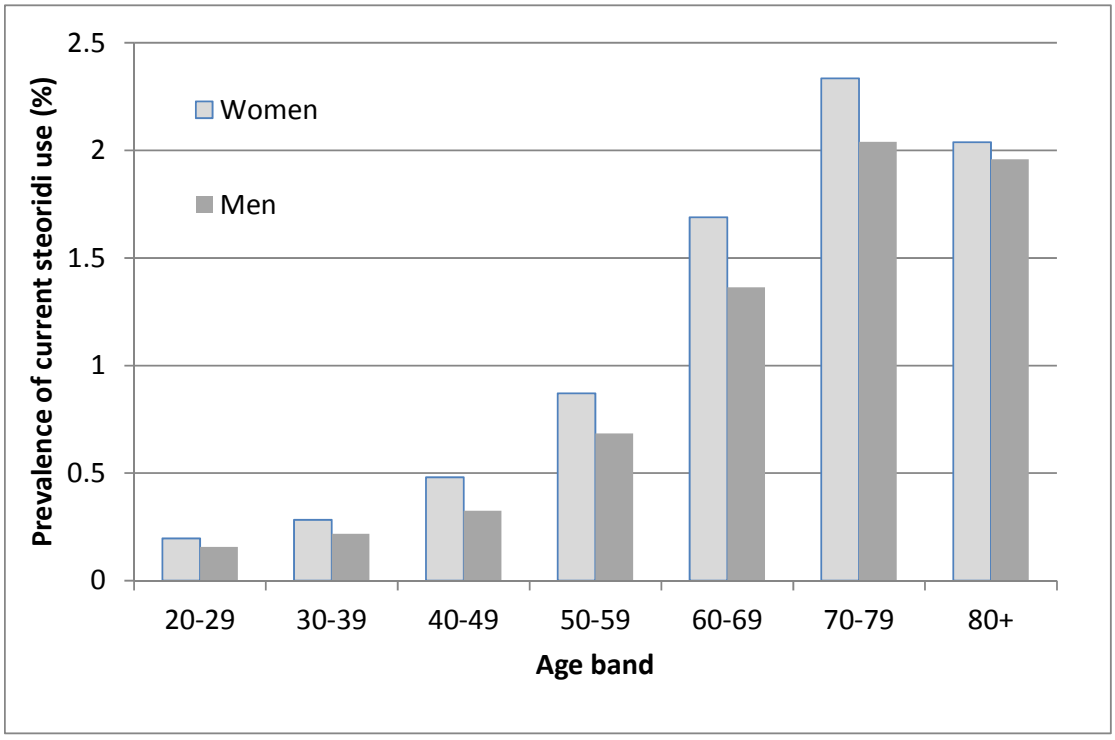


From Census 2011: Residence type by sex by age. [177] and Census 2011: Communal establishment management and type by sex by age. 2011.[178]

For steroid use, data published by van Staa et al suggest that the prevalence of current steroid use increases with age.[179] Their estimates were based on analysis of the General Practice Research Database (GPRD which is now called CPRD) which is a large database of GP records for UK patients. This provided a large retrospective cohort which is likely to be representative of the general population of England and Wales. Data on the prevalence of oral glucocorticoid use by gender and 10 year age bands were digitally extracted from a graph provided by van Staa *et al.*[179] The relationship between prevalence and age appear to follow a similar pattern for low, medium and high dose users. Data were only extracted for medium and high dose steroid users as this dose (>2.5mg prednisolone daily) matched that specified in the FRAX fracture risk algorithm. However, when these data were combined with the ONS data on the current age distribution within England to estimate the average prevalence across patients aged 30 years and over, this was substantially lower than the prevalence recorded in the QFracture database (0.95 % versus 2.2%). The difference may be due to the fact that we did not include low dose users from the van Staa estimates or that the QFracture data do not appear to relate to a specific dose of steroids. A more recent estimate of the prevalence based on UK GP records is provided by Fardet *et al.*[180] Whilst this didn't provide a breakdown of

the prevalence by age and gender, the overall prevalence of 0.79% for 2008 reported by Fardet *et al.* is closer to that reported by Van Staa *et al.* than the figure reported in the QFracture database. We therefore decided to use the combined data for medium and higher dose users provided by van Staa data et al to characterise the age and gender distribution of steroid use. Figure 77 shows age and gender specific prevalence estimates applied in the model for steroid use.

Figure 77: Prevalence of current steroid use: data from van Staa et al. combined for medium and high dose steroid users

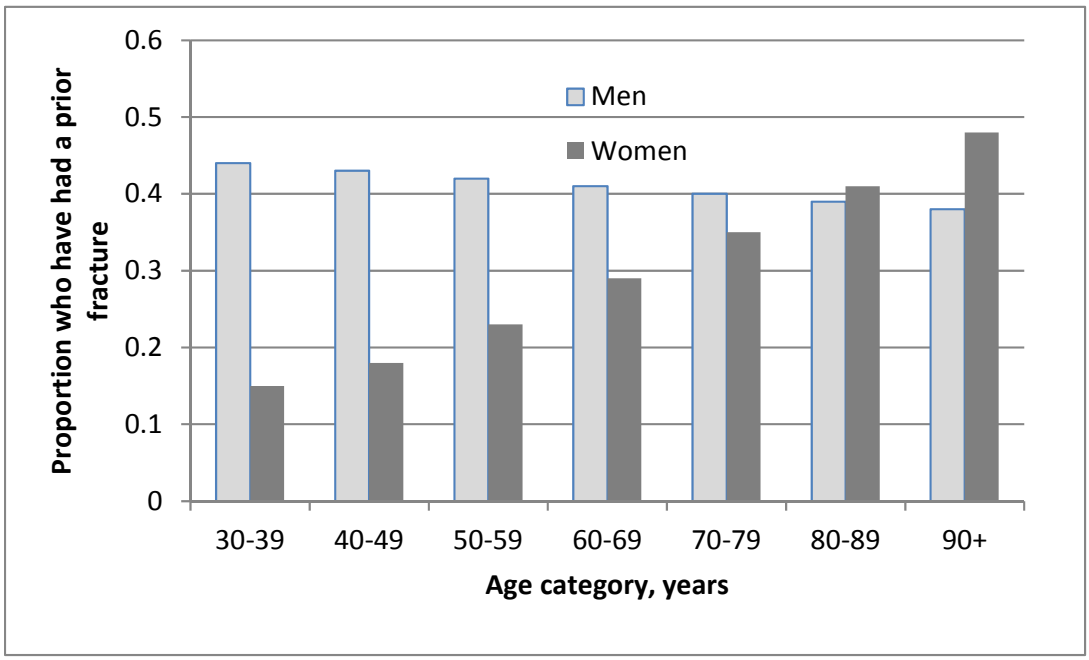


From van Staa *et al.* [179]

Data on the prevalence of previous fracture were taken from a meta-analysis by Kanis *et al.*[181] This data was selected as it provided data on the prevalence of having sustained a prior fracture reported by gender and 10 year age bands. The cohorts used to estimate the prevalence of prior fracture were the same cohorts used to estimate the impact of prior fracture on future fracture risk for the FRAX algorithm.[166] The prevalence of prior fracture is difficult to quantify as it depends on whether all prior fractures are included regardless of the site of fracture or the mechanism of injury. Whilst the definitions used varied across the multiple cohorts that informed the estimates from Kanis et al, the fact that these cohorts were then used to derive the impact of prior fracture on future fracture risk provides some consistency between the definition of prior fracture used for prevalence and for risk score calculation. The prevalence reported by Kanis *et al.* for each of the 10 year age bands, which

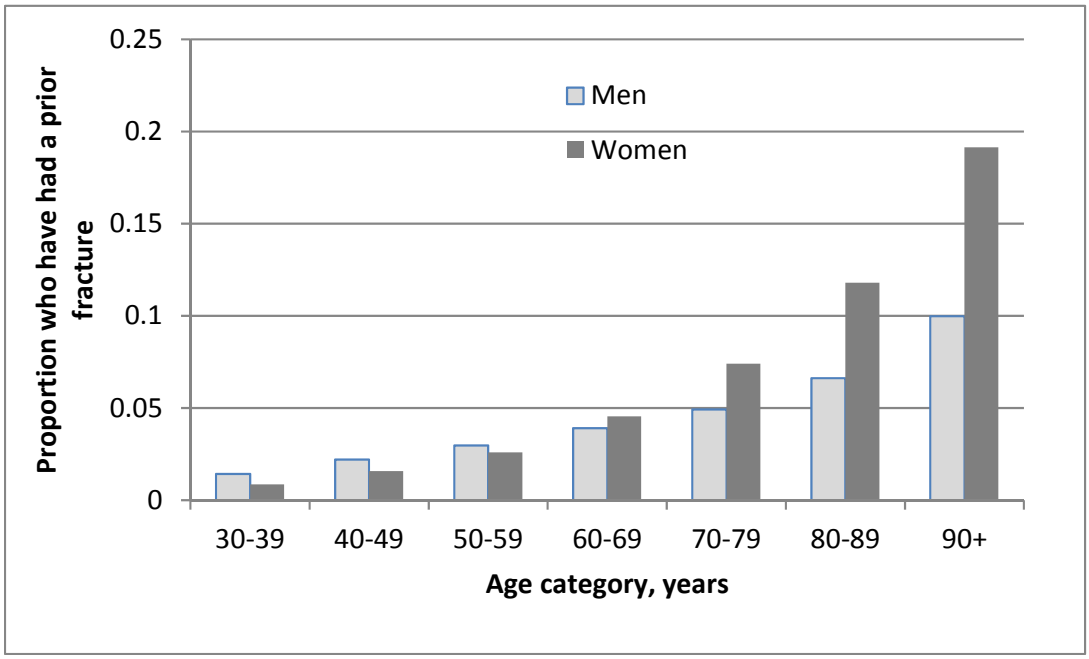
ranged from 15% at age 30 to 48% at age 80 in women, is much higher than that reported within the QFracture cohort (1.9% across a cohort aged ≥30 years).[167,181] An alternative estimate of the prevalence of prior fracture is provided by Scholes *et al.* who used data collected during the Health Survey for England (HSE) to estimate the prevalence of previous fracture in community dwelling people aged over 55.[182] They found a that the prevalence was 49% in men and 40% in women although this data relied on the individual's recall and didn't distinguish between fragility fractures and those occurring in early life or associated with significant trauma. Another source of evidence which can be used to cross-check the estimates provided by Kanis *et al.* are studies reporting the incidence of fracture by age. Prevalence can be estimated from these studies in an approximate manner by assuming that the prevalence of prior fracture at a particular age is equivalent to the cumulative incidence across all previous age-bands. Although under this assumption the prevalence may be inflated by multiple fractures occurring within the same patient, if these are reported separately in the incidence data. Data on the incidence of fracture by age and gender and the proportion of fractures that are fall-related (standing fall, fall down stairs, or fall from a low height) is provided by Court-Brown *et al.*[183] This was a prospective cohort study conducted in Scotland in 2010/11 which compared the rate of fractures presenting to the Royal Infirmary of Edinburgh to population estimates from the 2001 census to estimate incidence rates. Estimating the prevalence of fall-related fractures from these data by assuming that it is equal to the cumulative incidence in those aged over 35 provides prevalence data closer to that reported by Kanis *et al.* than that reported in the QFracture cohort. Therefore the data presented by Kanis *et al.* (Figure 78) were used in the model to sample the likelihood of an individual having a prior fracture.[181] A second incidence study by van Staa *et al.*[184] provides data on the incidence of fracture in England in a general practice (GPRD) cohort which examined over 20 million person-years of follow-up. Data on the proportion of fractures that were fall-related from the study by Court-Brown *et al.*[183] were applied to the incidence data reported by van Staa et al .[184] to estimate the incidence of fall-related fractures in an attempt to exclude fractures related to significant trauma such as road traffic accidents. Prevalence of a prior fracture after the age of 35 was then estimated by calculating the cumulative incidence from age 20 and these data are summarised in Figure 79. The prevalence estimated in younger age groups when using this method was lower compared with the data reported by Kanis *et al.* [181] This alternative estimate of the prevalence of prior fracture were applied in a sensitivity analysis to assess whether the cost-effectiveness of bisphosphonate treatment is sensitive to the prevalence of prior fracture in the population.

Figure 78: Proportion who have had a prior fracture by gender and age-band (data applied in basecase)



From Kanis *et al.*[181]

Figure 79: Proportion who have had a prior fracture by gender and age-band (data applied in sensitivity analysis)



Adapted from van Staa *et al.*[184] using additional data from Court-Brown *et al.* [183]

Swedish estimates for the incidence of fracture at different sites across genders and age-bands were then used to estimate the cumulative prevalence of fractures at various sites up to the start age for each age band.[173] These data were used to determine the distribution of prevalent fractures across different fracture sites as shown in Table 12. As the incidence data were presented for patients aged 50 years and over we have assumed that the distribution of prior fractures at ages 30 to 55 is equal to the distribution of incidence from ages 50 to 55. It can be seen that as the incidence of hip fracture rises with age, the proportion of prior fractures that have occurred at the hip increases with each increasing age category.

Table 12: Distribution of prevalent fractures across the four main osteoporotic fracture sites (within each gender)

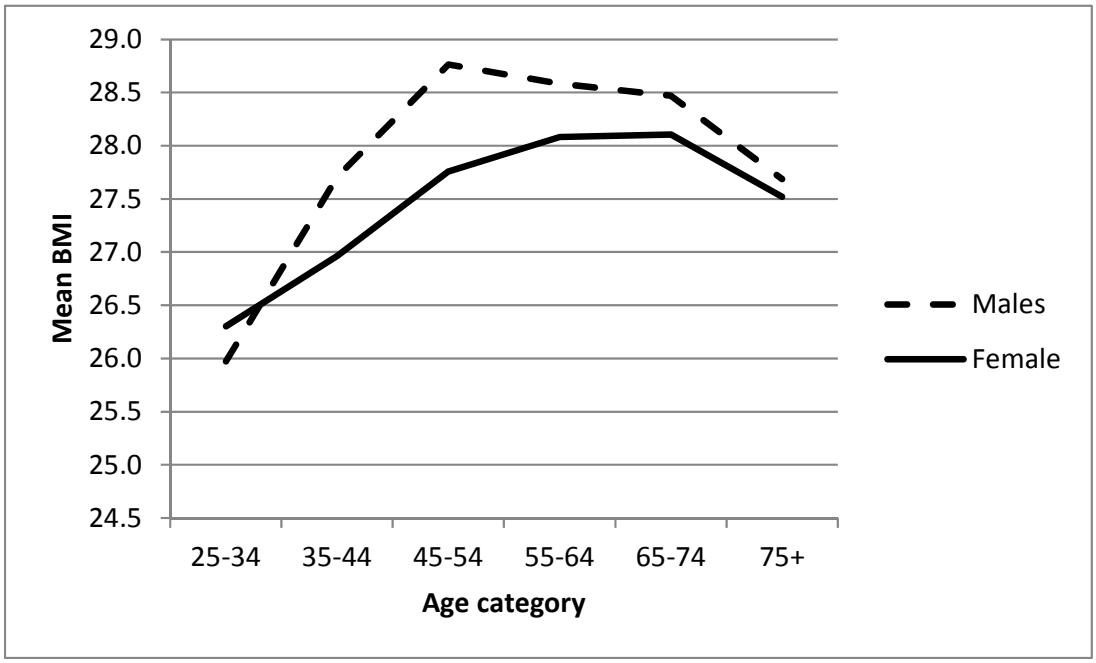
Fracture site	Age band							
	< 55	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Women								
Hip	6%	6%	8%	11%	15%	20%	27%	36%
Vertebral	22%	22%	20%	23%	23%	25%	25%	22%
Proximal humerus	17%	17%	16%	14%	16%	15%	15%	13%
Wrist	56%	56%	55%	52%	46%	40%	34%	29%
Men								
Hip	10%	10%	14%	18%	23%	29%	36%	44%
Vertebral	48%	48%	41%	41%	35%	36%	35%	32%
Proximal humerus	16%	16%	12%	12%	11%	13%	12%	10%
Wrist	25%	25%	33%	29%	30%	22%	17%	14%

Calculated from incidence data presented by Kanis et al[173]

Data are available from the Health Survey for England (HSE) on the average BMI for different ages and genders.[185] These data, presented in Figure 80, show that BMI varies with age. Whilst BMI is not expected to affect cost-effectiveness except through its influence on absolute fracture risk, it is considered to be an important risk factor particularly where BMD is unknown. A recent meta-analysis found that the relationship between BMI and fracture risk is much weaker after adjusting for BMD.[186] A significant positive correlation was also found in this study between BMI and BMD ($p < 0.001$; $r = 0.33$; 95% CI, 0.32–0.33). Given the significant correlation between these two variables and the fact that we are assuming that BMD is not available when fracture risk is first assessed, we decided to model the age variation in BMI as this may capture some of the underlying variation in BMD with age. However, we accept this will only capture a small proportion of the association between

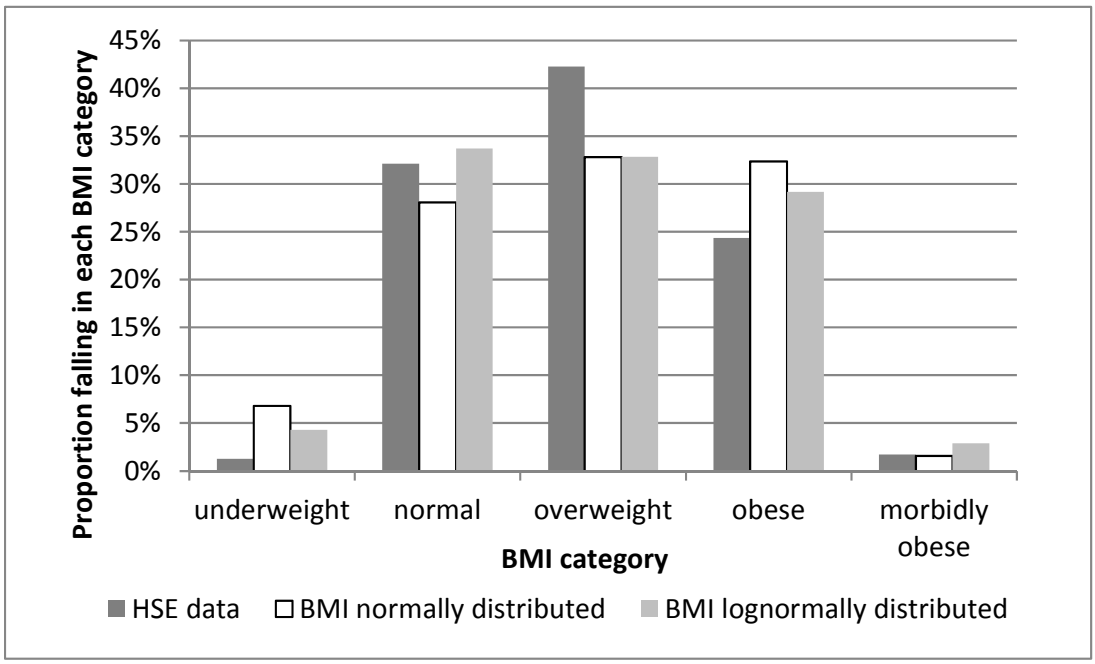
BMD and age. We decided to use the HSE data to characterise the mean BMI for different age bands and genders as these data allow the standard deviation to be calculated. However, they do not provide any information on the shape of the BMI distribution. We assumed that the BMI values were lognormally distributed as we found that assuming a normal distribution over-estimated the proportion falling within the underweight category. As it is the underweight group who are at particular risk of fragility fracture, assuming a normal distribution would have overestimated population fracture risk.[186] As can be seen in Figure 81, assuming a lognormal distribution still overestimated the proportion who were underweight but the difference was 3 fold rather than 5 fold.

Figure 80: Mean BMI by age and gender from 2012 Health Survey for England



Health Survey for England[185]

Figure 81: Proportion of men (adults aged over 16 years) falling into different weight categories



6.2.1.3 Treatment strategies

The model compares the following treatment strategies

- alendronate
- risedronate
- oral ibandronate
- i.v. ibandronate
- zoledronate
- no treatment

We assume that all patients will receive adequate supplemental calcium and vitamin D regardless of whether or not they are being treated with a bisphosphonate and therefore no cost is included within the model for calcium and vitamin D supplements.

We assume that the intended treatment duration is 5 years for alendronate, risedronate and ibandronate and 3 years for zoledronate. However, not all patients persist with therapy for the intended duration as previously discussed in section 5.2.2 which describes the clinical evidence on treatment persistence. The duration of treatment in the model was therefore set to the mean duration of persistence using data from the systematic reviews described in section 5.2.2. The highest quality systematic review was considered to be that by Imaz et al[187] which reported that the mean duration of treatment persistence of 184 days (95%CI 164 to 204) for oral alendronate, risedronate and ibandronate. Only one of the studies included in the meta-analysis of average persistence by Imaz *et al.* examined ibandronate with the rest considering alendronate and risedronate. However, the mean duration of persistence for monthly ibandronate was similar to the mean duration for weekly alendronate and risedronate (98 for ibandronate vs. 116 and 113 for alendronate and risedronate respectively). Therefore we decided to use the pooled estimate provided by Imaz *et al.* for all oral bisphosphonates.

The review by Imaz *et al.* did not provide any data on persistence in patients receiving i.v. bisphosphonate therapy.[187] However a review by Vieira et al[188] identified a cohort study (Curtis 2012[189]) in US Medicare patients which provided estimates of the mean number of infusions received for zoledronate and ibandronate.[189] It is noted that the duration of treatment with zoledronate estimated by Curtis *et al.* was considered by our clinical advisors to be low compared with their own experience of administering zoledronate within clinical practice. However, in the absence of an alternative estimate these data were used to estimate the mean duration of persistence with therapy for i.v. bisphosphonates. The full treatment effect was assumed to persist for 1 year after the last zoledronate infusion and 3 months after the last ibandronate infusion. Persistence data applied in the basecase model are summarised in Table 13. A sensitivity analysis in which we assumed full persistence with treatment for 3 years for zoledronate and 5 years for all other treatments was also examined.

The fall-off period was assumed to be equal to the duration of treatment for all treatments except zoledronate where a longer fall-off period was assumed. Clinical advice was that a 7-year fall off period could be assumed for 3 years of zoledronate treatment. We therefore assumed an approximate fall-off period of 2.33(=7/3) times the treatment period for zoledronate.

Table 13: Duration of persistence with treatment

Treatment	Mean duration of persistence with treatment	SE	Source
Alendronate, risedronate and oral ibandronate	184 days (0.5 years)	10 days	Meta-analysed estimate from Imaz 2010 systematic review[187]
Oral ibandronate	401 days (1.1 years)	15 days	Curtis 2012 [189]
Zoledronate	621 days (1.7 years)	6.5 days	Curtis 2012[189]

6.2.1.4 Estimating time to event from absolute fracture risk

The algorithm used by the QFracture tool to calculate the risk of fracture over varying time periods is publically available on the QFracture website (http://www.qfracture.org/). This algorithm was examined and was found to have the following form:

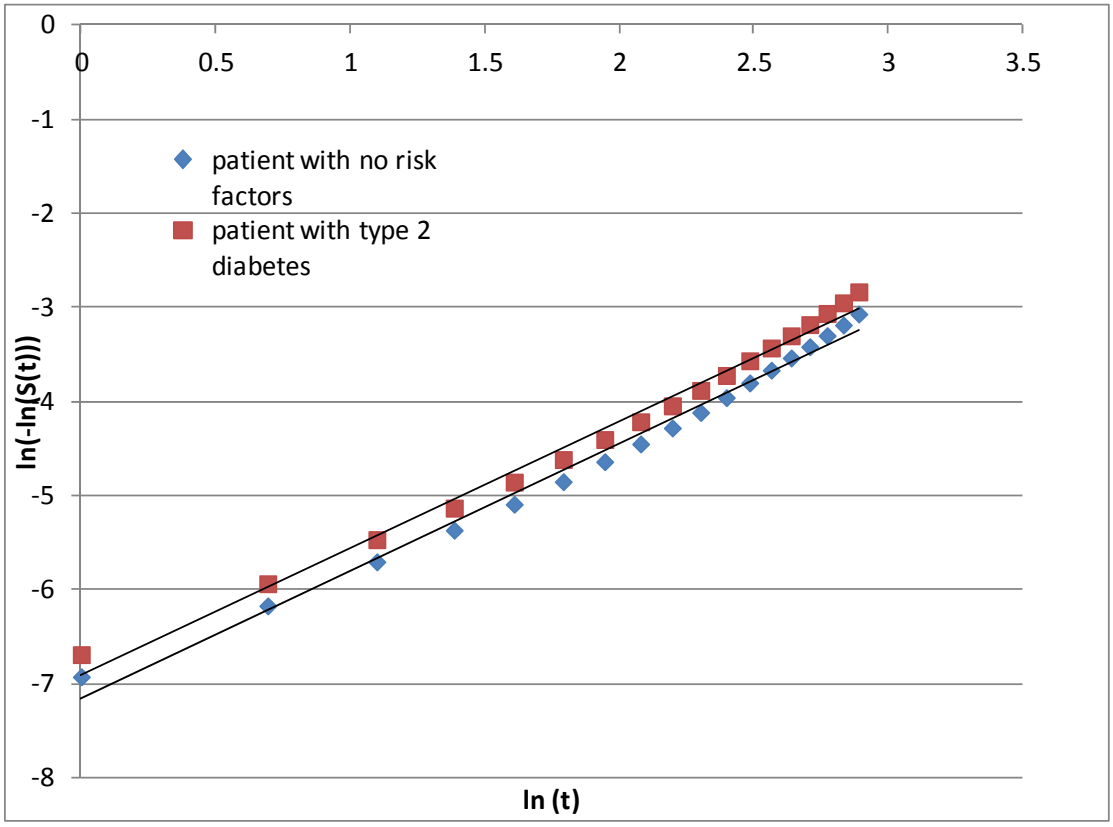
Cumulative risk over t years = $1- S_0(t)^{\exp(\eta)}$,

Where the parameter η is the risk modifying factor which adjusts for patient characteristics and S_0 is the underlying survival function. Different values of S_0 are defined according to the time frame (t) over which risk is to be assessed. The survival model used to estimate the risk modifying factor η is described as a Cox regression. In a Cox regression the values for S_0 do not have to follow any particular parametric form. However, when the S_0 values were plotted, to give the fracture free survival for patients without any risk modifying factors (η =0), it was noted that they appeared to be very smooth suggesting that it may be possible to fit a functional form to the underlying survival function. Given that the Weibull function (which includes the exponential function as a special case) and the Gompertz function are both compatible with a proportional hazards assumptions, we tested both of these parametric forms to see if they were suitable.

A plot of ln(-ln(S(t))) against ln(t) was produced to see whether the data were consistent with a Weibull survival curve. This was done for an example patient with the following characteristics: female; aged 50; BMI 24; no clinical risk factors. The same plot was then produced for a patient with type 1 diabetes but no other clinical risk factors and the same age and BMI to examine the impact of clinical risk factors on the shape of the plots. From Figure

82 it can be seen that the distance between the plots is constant for these two cases, as would be expected for a proportional hazards model, but neither plot is linear over the whole time period. The plots appear to be linear over short time periods (5 or perhaps 10 years) but the Weibull curve does not appear to be appropriate over longer time frames.

Figure 82: Plot to test suitability of Weibull survival curve*



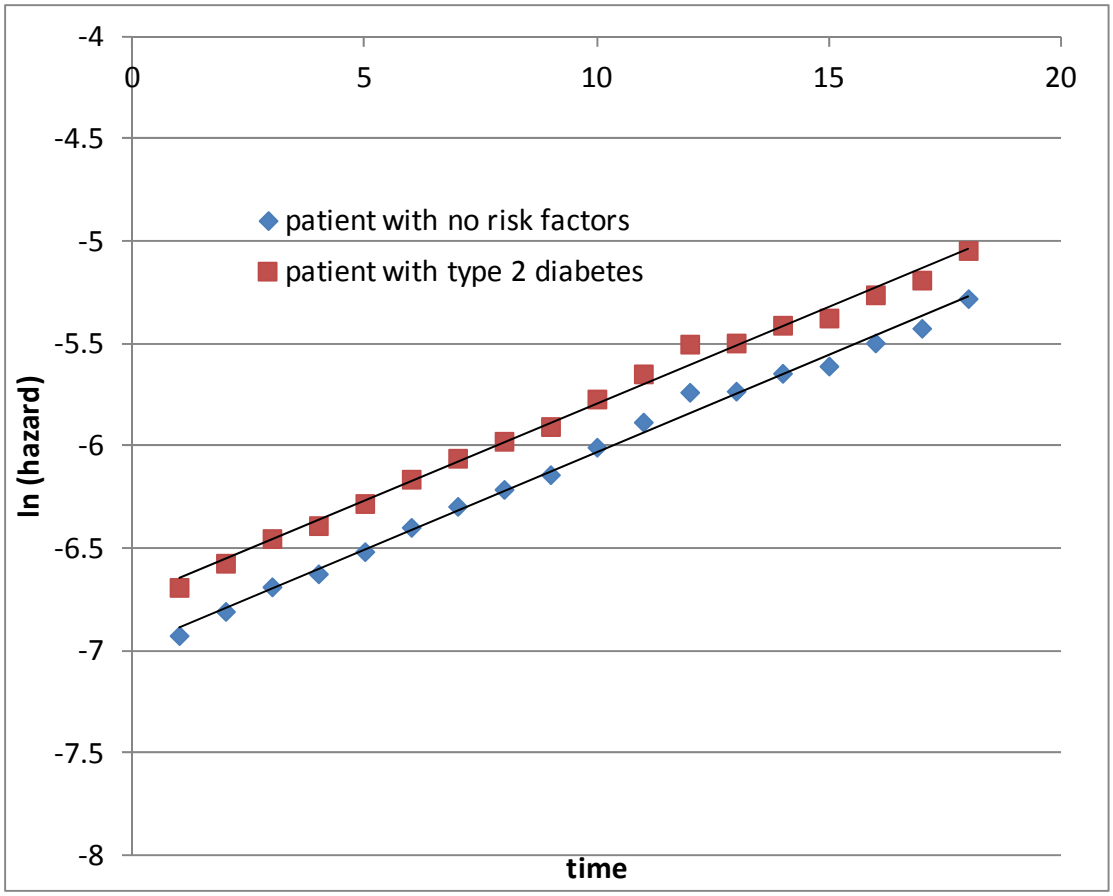
*Patient characteristics: female; aged 50; BMI 24; with or without type 2 diabetes

A plot of ln(hazard) against time was generated once again for a 50 year old female with BMI of 24 and either with or without type 2 diabetes as shown in Figure 83. This was found to be linear suggesting that the underlying survival function was consistent with a Gompertz distribution. We have therefore assumed that the underlying survival function follows a Gompertz distribution and used the linear fit for the ln(hazard) function to estimate the parameters for the Gompertz distribution in patients without any risk modifying factors (η =0). Table 14 shows the survival parameters for the underlying Gompertz distribution in males and females for the outcomes of survival free of osteoporotic fracture (hip, wrist, vertebral and proximal humerus) and survival free of hip fracture.

Figure 84 to Figure 87 shows the fit of the parametric curve against the survival data specified in the QFracture algorithm for each of these survival functions. It can be seen from the plots

that the parametric curves fit the data better in the first 10 years and that the parametric curves may underestimate long-term fracture risk. Whilst this was noted as a limitation, the good fit up to 10 years means that the rates are sufficiently accurate during the period in which drugs are assumed to affect fracture outcomes. An underestimation of the long-term fracture risk in the period after the drug efficacy is assumed to fall to zero is likely to affect all treatment strategies equally and therefore is not expected to significantly bias the estimates of cost-effectiveness. We therefore assumed that the fitted Gompertz curve could be used to estimate time to fracture for patients with no risk modifying factors.

Figure 83: Plot to test suitability of Gompertz parametric form*



*Patient characteristics: female; aged 50; BMI 24; with or without type 2 diabetes

Table 14: Parameters for fitted Gompertz functions in patients with no risk modifying factors (η =0)

Survival function	Gender	Alpha	Beta	R squared
Osteoporotic (hip, wrist, proximal humerus or vertebral) fracture	Female	Exp (-6.9499)	0.0947	0.9942
Hip fracture	Female	Exp(-9.4486)	0.1375	0.9963
Osteoporotic (hip, wrist, proximal humerus or vertebral) fracture	Male	Exp(-8.0425)	0.0908	0.9882
Hip fracture	Male	Exp(-10.228)	0.1454	0.9902

Figure 84: Gompertz fit for female patient with no risk modifying factors (η =0) for the outcome of any osteoporotic fracture (hip, wrist, proximal humerus, vertebral)

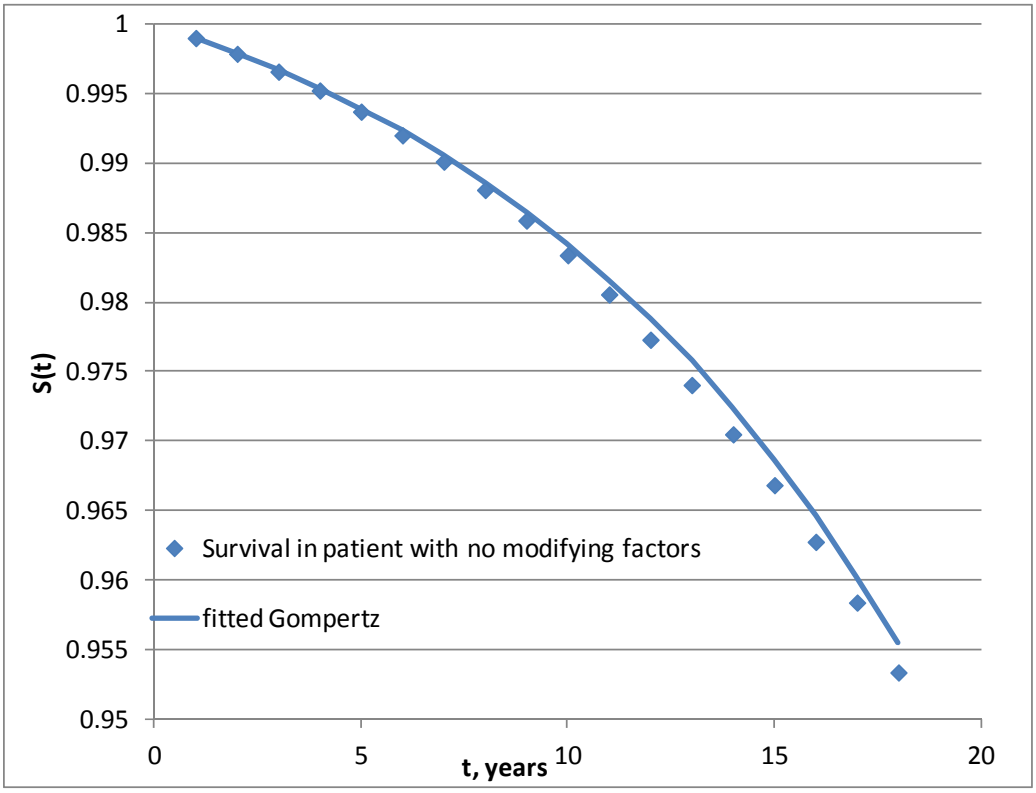


Figure 85: Gompertz fit for female patient with no risk modifying factors (η =0) for the outcome of hip fracture

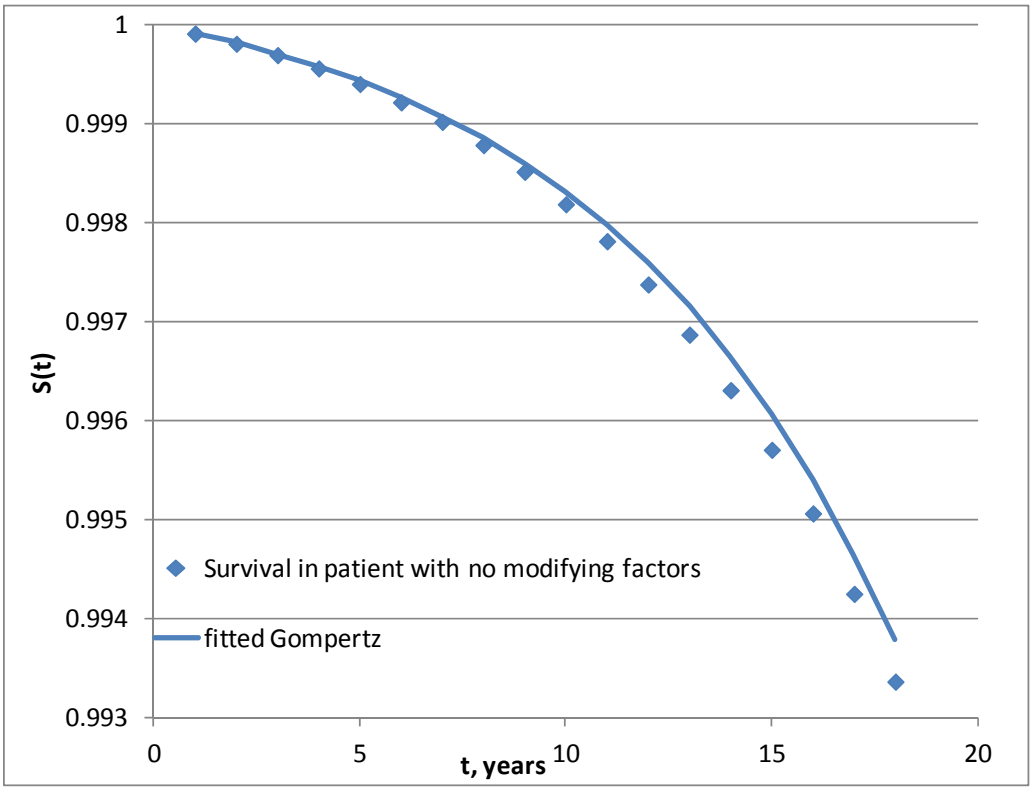


Figure 86: Gompertz fit for male patient with no risk modifying factors (η=0) for the outcome of any osteoporotic fracture (hip, wrist, proximal humerus, vertebral)

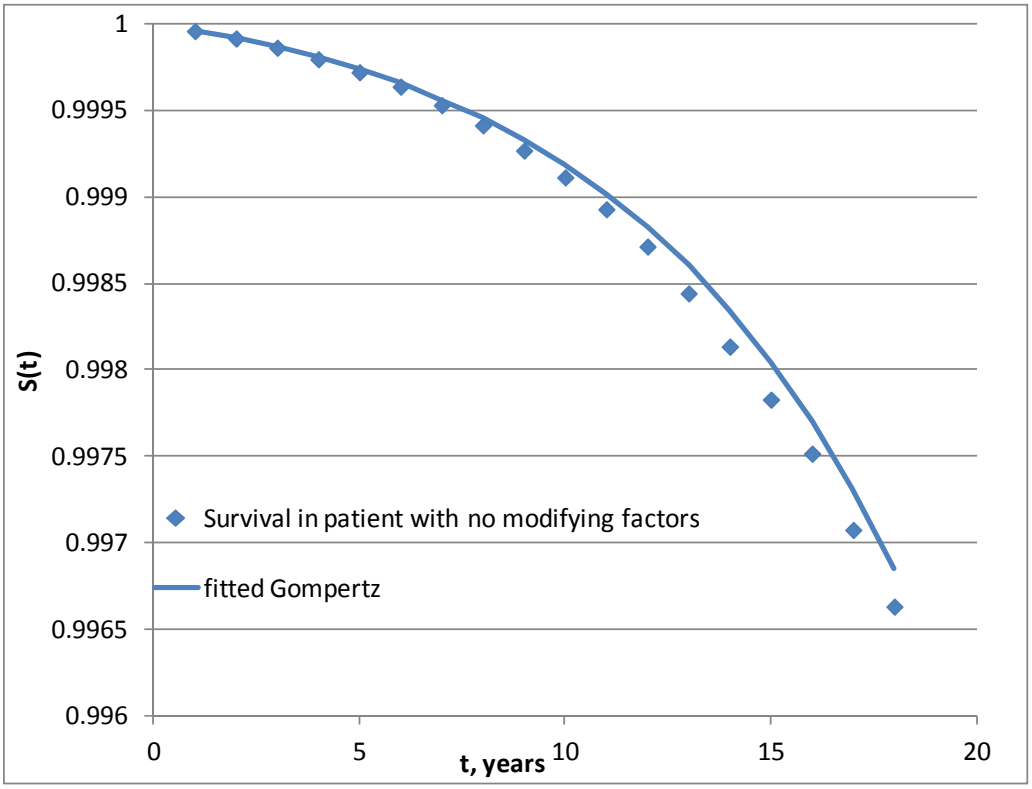
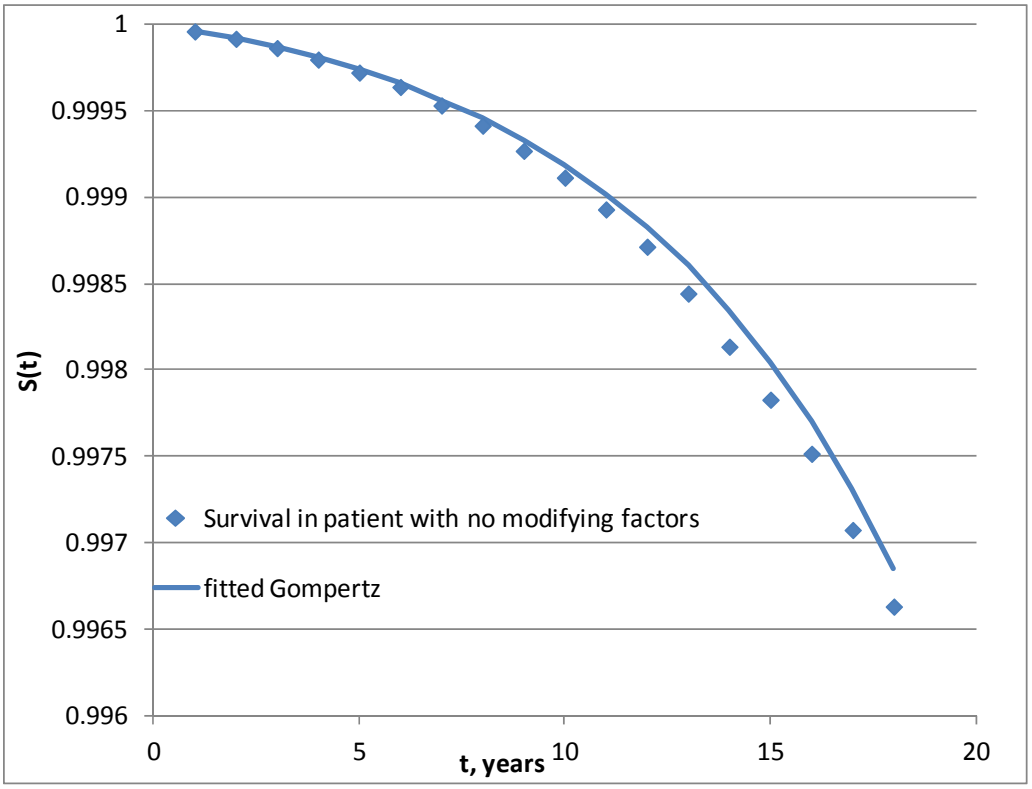


Figure 87: Gompertz fit for male patient with no risk modifying factors (η=0) for the outcome of hip fracture



QFracture does not provide individual predictions for each of the four major osteoporotic fractures (hip, wrist, vertebral and proximal humerus). Instead it provides an estimate of the absolute risk of fracture across all four fracture types. In order to provide an estimate of the time to fracture for each site, we multiplied the alpha parameter for the fitted Gompertz survival curve by the proportion of patients experiencing an incident fracture of that type. The proportions, shown in Table 15 were estimated from Kanis 2001 *et al.* [173] which provides the incidence of fractures in Sweden across different fracture sites by gender and age band.

Table 15: Proportion of major osteoporotic fractures occurring at each site by gender and age band*

Fracture site	**Age band (years)**							
	50-54	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-89**
Women								
Hip	6%	6%	11%	15%	21%	28%	38%	53%
Vertebral	22%	22%	19%	26%	23%	27%	25%	18%
Proximal humerus	17%	17%	15%	11%	19%	13%	14%	9%
Wrist	56%	56%	55%	48%	37%	31%	23%	19%
Men								
Hip	10%	10%	18%	24%	31%	38%	49%	57%
Vertebral	48%	48%	32%	40%	27%	39%	32%	28%
Proximal humerus	16%	16%	8%	11%	10%	16%	9%	7%
Wrist	25%	25%	41%	25%	32%	7%	9%	8%

*calculated from Kanis *et al. 2001*[173]

We used these site specific alpha values to generate samples from the Gompertz distribution for each fracture site and plotted a survival function for time to fracture at each site. To validate this approach, of apportioning the alpha value for major osteoporotic fracture across the four sites, we calculated the time to first major osteoporotic fracture from these site specific fracture survival curves and compared these to the survival from major osteoporotic fracture predicted by the QFracture algorithm. We found that the survival curves generated were comparable suggesting that this method of calculating site specific fracture curves is valid as can be seen from Figure 88.

However, as can been seen from Figure 89, when we compared the hip fracture data calculated from major osteoporotic fracture to the hip fracture survival estimates provided

directly from the QFracture algorithm we found that these did not match well over longer time frames (i.e. over 5 years). This can be explained by the fact that the beta value for the hip fracture specific Gompertz curve is higher suggesting a faster increase over time for hip fracture than is seen over all major osteoporotic fractures. We decided to use the hip fracture survival predicted by apportioning the major osteoporotic fractures in the basecase analysis as this would provide an estimate of major osteoporotic fracture that is consistent with the estimates from the QFracture algorithm. Furthermore the beta value for the Gompertz function for major osteoporotic fracture is likely in reality to be the average of a lower value for non-hip and a higher value for hip, but as the non-hip value could not be calculated we felt it was better to use the beta value for major osteoporotic fracture and apply it to all four fracture types in the basecase analysis. A sensitivity analysis was also conducted using the hip specific algorithm from QFracture for estimating time to hip fracture to see whether this had a significant impact on the cost-effectiveness.

Figure 88: Plot of survival curves for time to fracture based on 10,000 patients for each individual fracture site and for any major osteoporotic fracture.

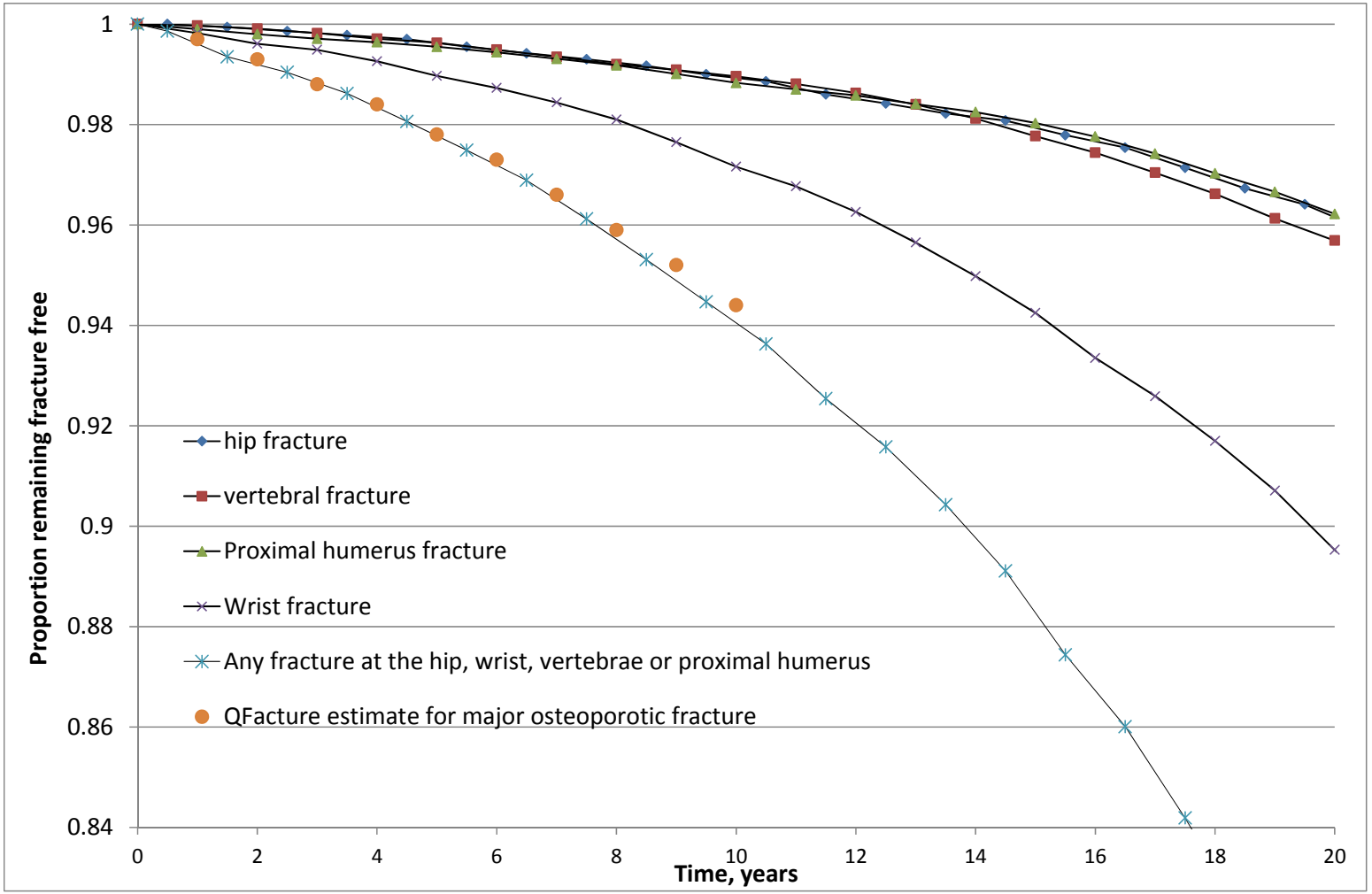
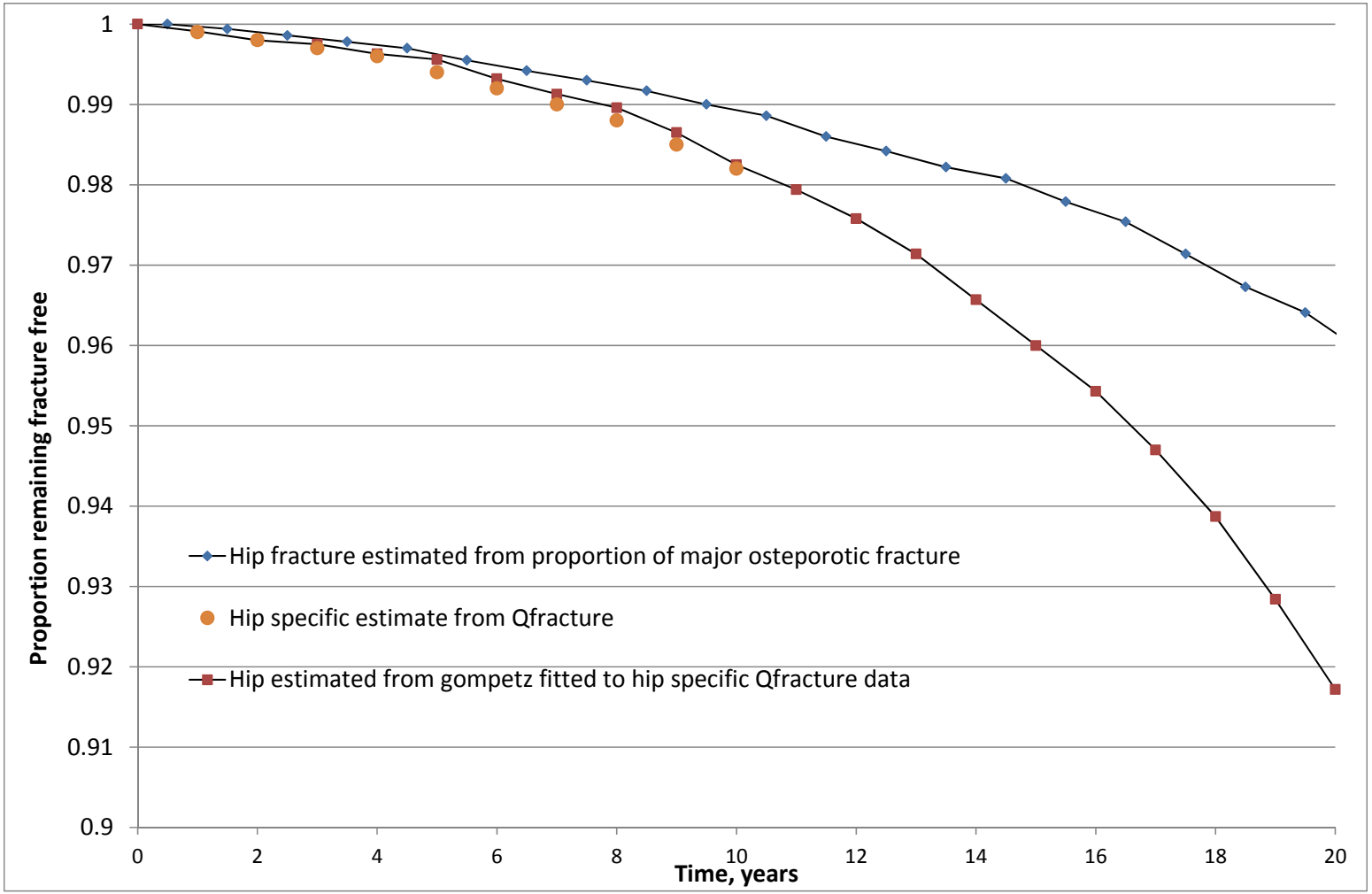


Figure 89: Comparison of survival curves from sampling directly from the Gompertz for hip fracture and from sampling hip as a proportion of the Gompertz curve for major osteoporotic fracture against the source QFracture data for hip



The following method was used to calculate time to event for each fracture type in the basecase analysis when assuming that patients have been assessed using the QFracture algorithm

1. Calculate the proportion, p, of major osteoporotic fractures that occur at the site of interest according to the person's age and gender

2. Calculate the risk score modifier, η, from the patient characteristics

3. Select the beta for the gender specific Gompertz survival curve

4. Select hazard ratio, HR, which incorporates any treatment effect from intervention

5. Calculate alpha for the gender specific Gompertz survival curve as follows:

   Alpha = alpha(for η =0) x p x exp(η) x HR

6. Sample time to fracture from Gompertz (alpha, beta)

A similar approach was not possible when estimating time to event using the estimates of absolute fracture risk provided by the FRAX algorithm. This is because the algorithm used to calculate absolute fracture risk within the FRAX tool is not publically available and therefore it wasn't possible to assess whether survival from fracture follows a particular parametric form. Instead we assumed the underlying shape of the survival curve for FRAX would be identical to that used in the QFracture algorithm. In effect this meant assuming a Gompertz curve is followed which has the same beta parameter as seen in the QFracture algorithm. In doing so we were then able to calculate the time to event for patients assessed using the FRAX tool by calculating the multiplier, Φ, which needed to be applied to the alpha value of the QFracture survival curve to provide the absolute risk of fracture at 10 years predicted by FRAX. In doing so we assumed that there is a constant hazard ratio between the number of events predicted by FRAX and the number predicted by QFracture across all time frames. From equations 22 to 24 below it can be seen that Φ can be calculated by comparing the absolute risk of fracture estimated by the two fracture risk tools.

Absolute risk at 10 years in FRAX;

$$FRAX(10)= 1- S_0(10)^{\Phi \exp(\eta)}, \quad (22)$$

Absolute risk at 10 years in QFracture;

$$QF(10) = 1-S_0(10)^{\exp(\eta)} \quad (23)$$

From this we can derive that;

$$\Phi = \ln(1-FRAX(10)) / \ln(1-QF(10)) \quad (24)$$

One of the complicating factors with this approach is that QFracture provides an estimate of fracture risk without the competing risk of mortality whereas FRAX provides an estimate of absolute fracture risk when taking into account the competing risk of mortality. Therefore at older ages, when the risk of mortality is higher, the FRAX algorithm will calculate lower estimates of 10 year risk that the QFracture algorithm. In was not possible to correct for this within our model as we did not have sufficient information regarding the competing hazard of death used within the FRAX algorithm to adjust the FRAX estimates to exclude the competing risk of mortality.

6.2.1.5 Incorporating the risk of fracture at other sites

Whilst several of the published cost-effectiveness analyses restricted the fracture types included to the four main sites (hip, wrist, spine and proximal humerus) [154,156,157] some of the studies incorporated fractures at additional sites [158-160] by grouping these with one of the four main fracture sites. The decision over which fractures to group together has in previous analyses been justified by the expectation of similar costs and disutilities across particular groups of fractures.[190] The groupings used were consistent across the three published cost-effectiveness analyses that incorporated additional sites. [158-160]

We decided to keep the groupings used in these three studies with one exception. These studies grouped pelvis fractures with hip fractures. Pelvis fractures associated with osteoporosis were considered by our clinical advisors not to be associated with an excess risk of mortality similar to that associated with hip fractures and the costs were also expected to be lower. Therefore pelvis fractures were grouped instead with proximal humerus fractures. The grouping of fracture sites used within our model was therefore as follows

- Femoral shaft grouped with hip
- Clavicle, scapula, rib and sternum grouped with wrist
- Tibia, fibula, pelvis and humeral shaft grouped with proximal humerus.

Both QFracture and FRAX use a clinical definition for vertebral fractures and therefore the rate of vertebral fractures predicted in our model is specific to clinical vertebral fractures. The cost and quality of life implications of morphometric vertebral fractures which are not clinically apparent are likely to be much smaller than for clinically apparent vertebral fractures. Therefore we expect that excluding morphometric fractures which are not clinically apparent from the model to have a small impact on the ICER. Previous analyses by Stevenson *et al.*(reported in Appendix 15 of their HTA monograph) suggest that the exclusion of morphometric fractures does not significantly bias the estimates of cost-effectiveness.[157]

The multipliers applied to the rate of hip, wrist and proximal humerus fractures to incorporate the additional fractures sites were calculated based on Swedish incidence data reported by Kanis *et al.*[173] and are shown in Table 16. These were applied in the model to the alpha parameter for the Gompertz sampling of time to fracture. The data from age band 50-54 were applied to those aged 30 to 50. The very high multiplier for wrist fractures in men is driven by a large incidence of rib fractures compared with wrist fractures in the data reported by Kanis *et al.*[173]

Table 16: Multipliers applied to the rate of hip, wrist and proximal humerus fractures to include fractures at other sites (calculated from incidence data reported by Kanis et al.)

Fracture site	Age band							
	50-54	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-89**
Women								
Hip	1.27	1.19	1.20	1.13	1.11	1.09	1.07	1.08
Proximal humerus	1.89	2.08	2.26	1.74	1.93	1.89	2.33	2.14
Wrist	1.49	1.57	1.37	1.70	1.61	2.23	2.50	3.56
Men								
Hip	1.36	1.36	1.26	1.18	1.15	1.09	1.05	1.05
Proximal humerus	1.52	1.52	1.84	1.68	1.67	1.58	1.78	2.09
Wrist	5.36	5.36	6.89	4.49	4.57	12.83	6.06	15.41

From Kanis *et al.* [173]

6.2.1.6 Applying hazard ratios for treatment to the estimates of time to fracture

As we have assumed a Gompertz underlying survival function for time to fracture, and this is a proportional hazards model, the HR for treatment can be applied directly to the alpha parameter as described above. When taking a proportional hazards approach the treatment effect, as measured by the HR, is assumed to be constant over the entire duration of the survival curve. However, bisphosphonates are commonly only given for a few years and therefore we needed the model to allow for a fall-off in treatment effect after treatment is finished. For patients who complete the intended treatment period (5 years for all bisphosphonates except zoledronate) we have assumed a linear fall off in HR for each year from years 5 to 10 such that the HR at 10 years is 1. For zoledronate we have assumed a 3 year treatment period and a linear fall-off in treatment effect from years 3 to 10 such that the HR is 1 at year 10. This has been done by re-sampling the time to fracture at the end of the treatment period and applying a HR modified to account for the fall-off in treatment from years 5 to 10. The hazard ratio is modified by taking the average HR for full treatment effect and zero treatment effect. This modified HR is applied for the duration of the fall-off period. Whilst this linear approximation may underestimate the treatment effect in the early years after stopping and overestimate it in the latter years, it should provide the correct treatment effect on average over the fall-off period. Adding more dummy events to update the HRs at more frequent intervals over the fall-off period was avoided as it would reduce the computational efficiency of the model.

The time to fracture is resampled at the end of the fall-off period with a HR of 1 applied thereafter. As the hazard is assumed to increase over time in a Gompertz survival curve, the patient's age is updated prior to resampling the time to fracture resulting in a new alpha value in the Gompertz function. We noted that he QFracture algorithm does not appear to be internally consistent when applied at different ages. For example, the 1 year risk of fracture in a 55 year old is lower than the 1 year risk of fracture predicted for the 5th year in a patient aged 50. Given this internal inconsistency within the QFracture algorithm our method of resampling at 5 and 10 years results in a stepped linear function for the ln(hazard) even when the HR is held constant over the whole modelled timeframe. However, this method maintains the proportional hazards assumption within each step. This can be seen in Figure 90 where the diamonds and squares show the stepped ln(hazard) function which results from resampling at 5 and 10 years when applying a constant HR of 2 or 1 respectively. It can be seen that the gap between the diamonds and square is constant across the whole timeframe as would be expected for a proportional hazards model. Figure 91 demonstrates the additional effect of modifying the HR at 5 and 10 years to allow for reduced treatment effect during the fall-off period and no treatment effect beyond the fall-off period. It can be seen that this brings the ln(hazard) function for the treated patients (with treatment associated with a HR of 2 in this example), shown by the squares down to match that of the no treatment group (constant HR=1 across all years), shown by the diamonds from 10 years as would be expected. It should be noted that the squares and diamonds in Figure 91 do not match exactly as the graphs are based on stochastic time to event estimates but we would expect them to match exactly if an infinite number of samples were used to derive the plotted points.

In those scenarios where we assume that patients do not persist with treatment for the full 5 years (or 3 years for zoledronate), we have used additional dummy events at 5 and 10 years to ensure that all patients receive an updated estimate of fracture risks at these time points.

Figure 90: Plot showing how resampling at 5 and 10 years results in a stepped ln(hazard) plot but maintains the gap associated with the HRs

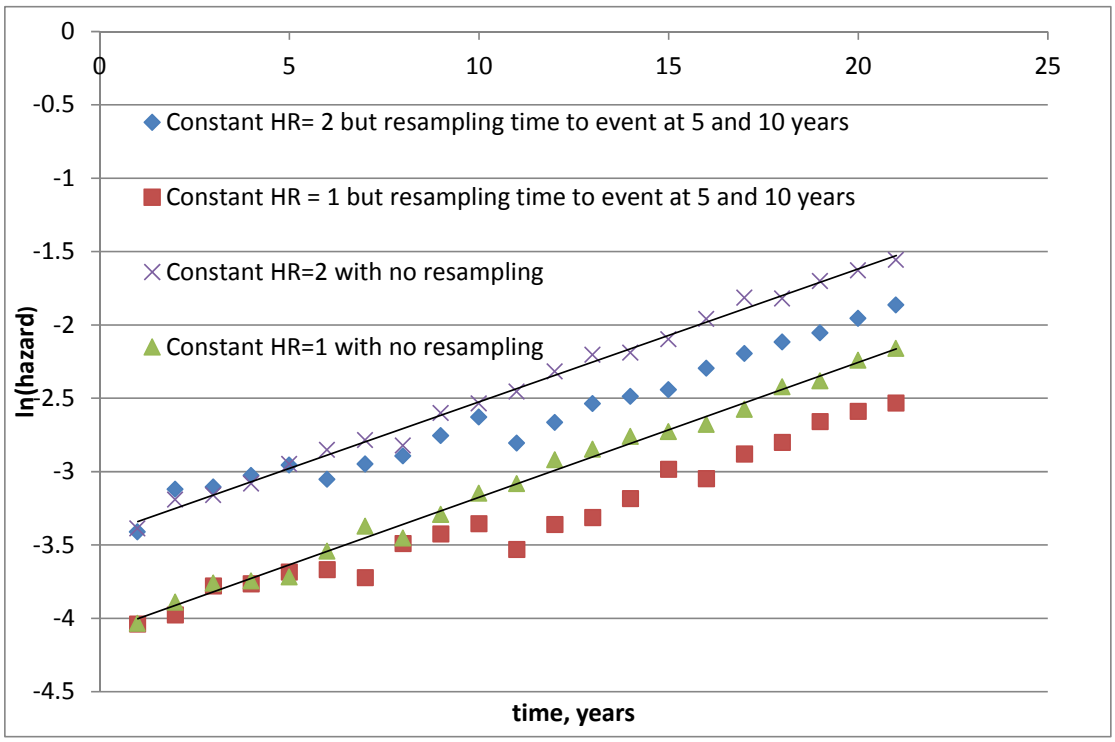
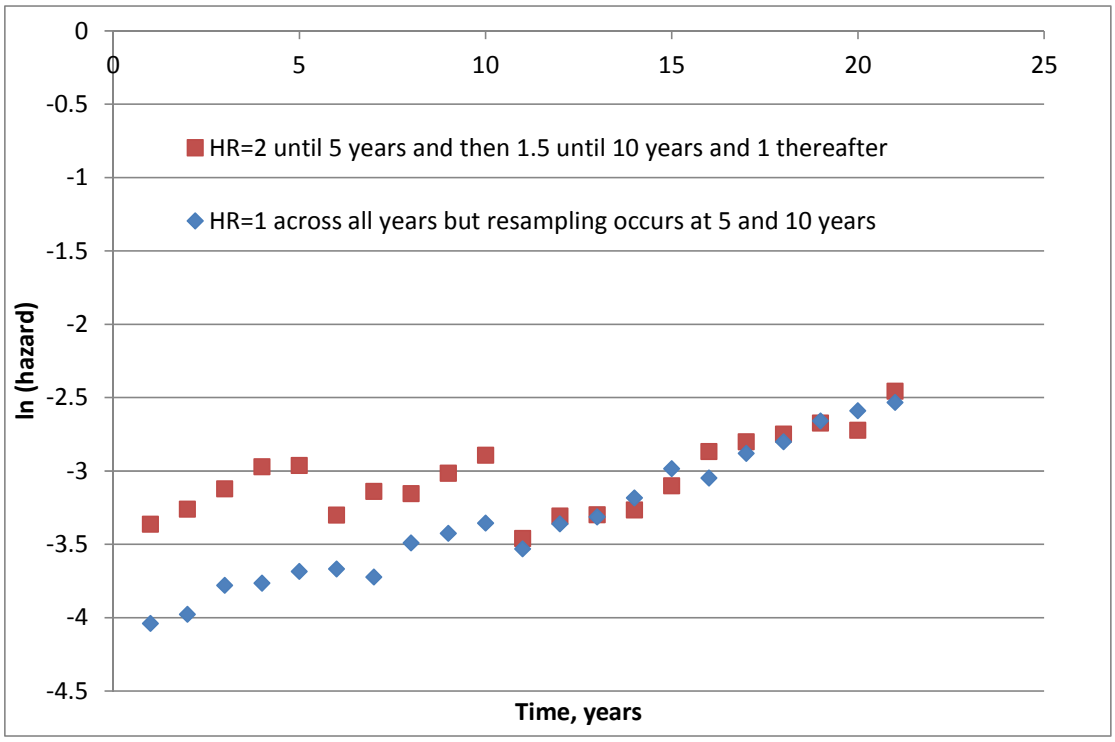


Figure 91: Plot showing the effect of adjusting the HRs to reflect falling treatment effect during the fall-off period (5-10 years) and at the fall-off period (10 years)



6.2.1.7 Efficacy estimates

Fracture data have been synthesised using a network meta-analysis model including all studies defined by the inclusion/exclusion criteria (i.e., males and females; steroid users and non-steroid users; confirmed low BMD or BMD unknown). The resulting measure of treatment effect was a hazard ration (HR) for the effect of each bisphosphonate relative to placebo together with an estimate of the between study standard deviation.

The network meta-analysis described in Section 5.2.2.1 of this assessment report has been used to generate the joint predictive distribution of the HR for each treatment compared with no treatment in a new study; this acknowledges heterogeneity in the effect of each treatment depending on the characteristics of patients included in the studies. These relative treatment effects have been applied consistently across the whole modelled population within the economic analysis.

Absolute effects of treatment predicted by the economic model (e.g. number needed to treat) vary across the population due to some patients having a higher absolute risk of fracture based on either the QFracture or FRAX score

The effect of treatment on hip fracture was estimated from studies reporting hip fracture data. The effect of treatment on vertebral fractures was estimated from studies reporting all vertebral fractures (i.e., clinical and morphometric) because not all studies (i.e., treatments) reported outcomes for clinical vertebral fracture. The effect of treatment on proximal humerus fractures was estimated using all non-vertebral fractures as a proxy because too few studies reported data for fractures specifically at the proximal humerus. Evidence on the effect of treatment on wrist fractures was available for all treatments except for zoledronate. The effect of zoledronate was estimated from the statistical model using the predictive distribution of a new bisphosphonate in a population of bisphosphonates.

The efficacy evidence from oral daily ibandronate (2.5mg) has been applied to both monthly oral ibandronate (150mg) and quarterly i.v. ibandronate (3mg) where no alternative fracture data were available for these licensed dosing regimens as the monthly oral and quarterly i.v. doses were licensed based on their non-inferiority in lumber spine BMD outcomes when compared with the daily ibandronate treatment regimen.[45,47,49,191,192] Where there were fracture data available for monthly oral ibandronate but none for quarterly i.v. ibandronate or daily oral ibandronate we have assumed that the data from the monthly oral treatment can be applied to the i.v. treatment regimen. This was considered to be reasonable as both the oral monthly dose and the quarterly i.v. dose were licensed based on non-inferiority compared

with the daily oral dose for lumbar spine BMD outcomes.[191,192] Our own analysis of the femoral neck BMD data for these treatments would support this assumption of similar treatment effects for oral monthly ibandronate and quarterly i.v. ibandronate.

Fractures occurring at sites other than one of the four main osteoporotic fracture sites have the efficacy applied according to the site groupings previously described. i.e. hip fracture efficacy data are applied to other femoral fractures, wrist fracture efficacy data are applied to scapula, clavicle, ribs, sternum, and all non-vertebral fracture efficacy data are applied to tibia and fibula, pelvis and humeral shaft.

The hazard ratio is assumed to be constant over the duration of the treatment period and then to fall linearly over the fall-off period reaching no effect by the end of the fall-off period. The linear fall-off is approximated by applying the average HR of full and zero treatment effect for the duration of the fall-off period.

The HRs applied in the basecase are shown in Table 17. The median HR estimated by the NMA were used in the deterministic analysis and in the PSA analysis the CODA samples from the NMA were used as these preserve the underlying joint distribution.

Table 17: HRs applied in the deterministic analysis

	Hip	**Vertebral**	**Proximal humerus**	**Wrist**
Alendronate	0.78	0.45	0.80	0.83
Risedronate	0.82	0.51	0.71	0.76
Ibandronate (oral)	0.87	0.45	0.80	0.83
Ibandronate (i.v.)	0.87	0.47	0.92	0.83
Zoledronate	0.94	0.41	0.75	0.81

6.2.1.8 Adverse event estimates

Adverse events associated with bisphosphonate treatment were not consistently incorporated in economic analyses included in our review. Stevenson *et al.*[157] did not include any adverse events in the model reported in their 2005 publication, but a later DSU report by Stevenson

describes additional analyses in which adverse events were included.[193] Both Kanis *et al.*[155] and Borgstrom *et al.*[154] used the assumptions described in the DSU report by Stevenson within sensitivity analyses but neither included adverse events in their basecase. The remaining published analyses[156,158-160,163] did not include adverse events.

Stevenson used data from prescription-event monitoring studies identified in a systematic review by Lloyd *et al.*,[124] to determine the rate of upper GI problems in patients treated with oral bisphosphonates. In the DSU report Stevenson assumed 2.35% of patients required a GP appointment and a course of H2 receptor antagonists due to GI adverse effects in the first month of therapy and 0.35% thereafter.[193] These patients were assumed to have a HRQoL decrement of 9% (utility multiplier of 0.91from Groeneveld *et al.*[194]) for the full month which was described by Stevenson as a deliberately pessimistic assumption which aimed to counterbalance the fact that no other adverse events, such as nausea, had been included). Lloyd *et al.* also reported that other cohort studies found that 30% of patients starting alendronate may report gastrointestinal adverse effects.[124] A sensitivity analysis using a higher rate of adverse events (24%) in the first month of alendronate treatment was considered by the Technology Appraisal Committee when formulating recommendations for TA160 and TA161. [24,30]

Our review of systematic reviews examining adverse events did not identify any systematic reviews which examined GI adverse events that were published more recently than the review by Lloyd *et al.*[124] The prescription-event monitoring studies identified by Lloyd *et al.* found a greater incidence of dyspeptic conditions in the first month of treatment for alendronate and risedronate (3%) compared to later months (1%).[124] This was considered by our clinical advisors to be low compared to the rates they saw in clinical experience which were estimated to be around 20%

All three oral bisphosphonates were found to have similar rates of GI symptoms to placebo in RCTs. Furthermore, prescription-event monitoring data and data from two head-to-head RCTs suggest similar rates of GI symptoms for alendronate and risedronate. The submission by Actavis cited a study by Ralston *et al.*[125] which concluded that switching patients who are stabilized on risedronate to alendronate is associated with an increased risk of GI adverse effects. However, this evidence was not considered to be directly applicable to the question of whether adverse events are more common when initiating treatment with alendronate or risedronate in patients without prior treatment with bisphosphonate. Limited data were available to assess whether monthly formulations result in a lower incidence of GI symptoms than weekly formulations, but the review by Bobba *et al.* stated that increasing the dosing

interval to weekly or monthly intervals does not appear to change the rates of GI adverse events when compared to daily dosing for any of the three oral bisphosphonates.[195] Therefore the rates of adverse events for alendronate from prescription-event monitoring studies have been applied consistently to all oral bisphosphonates. Our clinical advisors informed us that clinical experience would suggest that upper GI symptoms are most problematic for alendronate with risedronate being less problematic and ibandronate even less so due to less frequent dosing. However, as this evidence was anecdotal they considered it reasonable to assume equivalent adverse events for the oral bisphosphonates.

In the model we applied the data on dyspeptic conditions from prescription-event monitoring studies described by Lloyd *et al.*[124] and assumed that 3% of patients starting treatment with an oral bisphosphonate experience GI symptoms requiring a GP appointment and prescription of a H2 receptor antagonist in the first month of treatment. A sensitivity analysis was also conducted examining a rate of 30% in the first month to reflect the higher rates observed in some observational studies as described by Lloyd *et al.*[124] Clinical advice was that proton pump inhibitors are usually prescribed instead of H2 receptor antagonist despite a caution in the BNF regarding the potential for an increased fracture risk for proton pump inhibitors.[196] However, as generic lansoprazole is similarly priced to generic ranitidine we have assumed for simplicity that all patients receive a H2 receptor antagonist. Total cost per patient experiencing a GI adverse event was assumed to be £46.76 (£45 for GP appointment and £1.76 for generic ranitidine.)[196] We have applied the same assumptions on disutility as Stevenson which we calculate to be equivalent to a QALY loss of 0.0075 per patient experiencing GI symptoms. We have applied this as a fixed QALY decrement at the start of the model without adjustment for baseline health utility.

In our review of adverse events, flu-like symptoms were found to be significantly higher for patients treated with zoledronate than placebo. Whilst none of the RCTs or observational studies reported flu-like symptoms for i.v. ibandronate, the SmPC for Bonronat (branded i.v. ibandronate) describes influenza like symptoms that resolve after “a couple of hours / days” as a common side effect affecting up to 1 in 10 people. A study by van Hoek *et al.*[197] reports the utility for influenza like illnesses as being 0.34 compared to a baseline (no flu-like symptoms) of 0.97 based on EQ-5D scores in a cohort of 655 patients with influenza-like illness. Based on these estimates, we considered that a utility multiplier of 0.30 would be reasonable for flu-like symptoms. We have assumed a disutility of 0.30 for 3 days for flu-like symptoms associated with i.v. bisphosphonates which is equivalent to a QALY loss of 0.005. This has been applied as a fixed QALY decrement at the start of the model without adjustment for baseline utility. We took the rate of influenza-like symptoms to be the rate of

pyrexia reported in the HORIZON-PFT study (Black 2007) as this was the largest RCT reporting data on flu-like symptoms and pyrexia was more common than other flu-like symptoms (headache / chills). The 14% difference between pyrexia rates for zoledronate compared with placebo was applied to patients receiving either i.v. zoledronate or i.v. ibandronate. These were only applied for the first infusion to reflect the fact that these rates were measured over the whole trial period (36 months) and therefore applying them repeatedly would overestimate the incidence of flu-like symptoms. Furthermore, it is likely that patients who experience significant side-effects are more likely to be in the group who do not persist with treatment so repeated episodes of significant disutility are unlikely.

6.2.1.9 Estimating time to non-fracture related mortality

Gender specific UK lifetables were used to provide an empirical estimate of the likelihood of death for each year after the start of the model.[171] This was calculated based on the age of the patient. So for a patient aged 30 the likelihood of death (denoted by d_x within the lifetables) between each birthday from the age of 30 to 100 was used to estimate the empirical distribution of survival times. Similarly for a patient aged 90 the likelihood of death between each birthday from age 90 to 100 was used. This method assumes no survival beyond age 100 as this is the limit of the data provided in the lifetables. The time horizon of the model was therefore set to equal 100 minus the starting age, giving a variable duration modelled depending on the patient's start age. The data used to estimate time to non-fracture related death were not varied in the PSA.

6.2.1.10Mortality after hip fracture

A systematic review by Abrahamsen *et al.* examining the relationship between hip fracture and mortality found that patients with hip fracture experience a high mortality rate which is at least double that experienced by age matched population norms.[198] Abrahamsen *et al.* also noted that whilst the highest excess risk appears to be in the first 6 months following fracture, many of the studies they examined found an increased risk that persisted for a number of years. Age and gender were both found to be important predictors of post fracture mortality supporting the use of age and gender specific estimates within our model.

Whilst there is clear evidence of excess mortality following hip fracture compared with general population norms, the extent to which underlying conditions contribute to the excess mortality associated with hip fracture is unclear. [198] Underlying health conditions, which may be more prevalent in patients experiencing hip fracture than in age and gender matched population norms, may contribute to mortality independently of the fracture itself confounding the relationship between fracture and mortality. Kanis *et al.*[199] found that 17% to

32 % of deaths following hip fracture were causally related to fracture, whereas Parker and Anand estimated that 25% of deaths were directly attributable to hip fracture with a further 42% possibly attributable to hip fracture.[200] A study by Tosteson *et al.* which was able to adjust for a number of prognostic factors including pre-fracture health status, found that excess mortality was limited to the first 6 months after fracture.[201]

To populate the model, data was needed on the absolute risk of mortality following hip fracture that is directly related to the hip fracture and therefore potentially avoidable by treatment to prevent fractures. Age and gender specific estimates were sought due to these being important risk modifying factors identified in the systematic review by Abrahamsen *et al.*[198] UK estimates were also considered preferable as these are more likely to be representative of the population likely to be affected by NICE guidance. Of the studies included in the review by Abrahamsen, 10 reported results for UK cohorts.{Allaf, 2004 1133438 /id;Deakin, 2007 1133439 /id;Goldacre, 2002 1133440 /id;Heikkinen, 2001 1133441 /id;Holt, 2008 1133428 /id;Holt, 2008 1133427 /id;McColl, 1998 1133442 /id;Parker, 1991 1133420 /id;Roberts, 2003 1133423 /id;Wood, 1992 1133443 /id} The majority of these studies do not report data on the absolute risk stratified by age and gender. Holt *et al.* provides graphs of survival at 120 days for different genders and age bands.[207] Deakin *et al.* provides age, but not gender specific estimates of mortality at 30 days and 1 year rates.[203] Parker and Anand provide age specific mortality rates but these aren't reported separately for males and females.[200] Only one study, by Roberts *et al.*, provides age and gender specific mortality rates and these are provided at 30, 60 and 365 days.[209] This study used data from the Oxford record linkage study which comprises anonymised abstracts of hospital statistics linked to death certificates. The population examined by Roberts *et al.* was 32,590 people aged 65 years and over who were admitted to hospital as emergencies with fractured neck of femur between 1968 and 1998. Mortality rates were compared over 6 time windows between 1968 and 1998 and absolute mortality rates are provided for the cohort admitted with fracture between 1984 and 1998.

The studies included in the review of published cost-effectiveness analyses were also examined to determine the source of data used. Stevenson *et al.*[157] used unpublished estimates from the Anglian audit of hip fracture which were reported for several different age bands and adjusted these to remove those deaths not causally related to hip fracture using the data from Parker and Anand.[157,200] Strom *et al.*[156] Borgstrom *et al.*[154] and Kanis *et al.* (2007) [159] used data from Sweden[199,211,212] rather than data from the UK. Van Staa *et al.*[158] estimated excess mortality rates from a UK database of general practice patients (GPRD which is now called CPRD) and absolute rates are presented by age band, but this cohort was restricted to

postmenopausal women. Van Staa *et al.*[158] used a Cox proportional hazards model to compare 1-year mortality rates for those with fracture and controls without fracture, who were matched based on age, GP practice, and calendar time. Similar methods were used in another of the included cost-effectiveness papers, Van Staa *et al.*,[160] which identified cases and controls from the same UK database but examined a population treated with steroids. However, this paper did not report the absolute mortality risks calculated.[160] No additional studies were identified from the papers by Kanis *et al.* (2008) and Borgstrom *et al.*(2006).[155,163]

The age and gender specific mortality rates reported by Roberts *et al.*[209] for 1 year were much higher than the excess rates reported by Van Staa *et al.*[158] This is to be expected because the estimates from Van Staa *et al.* [158] are the excess mortality rates compared with age and gender matched controls whereas the estimates reported by Roberts *et al.*[209] are raw mortality rates. As our aim was to include only the excess mortality associated with hip fracture in our model, the rates reported by Van Staa *et al.* [158] were incorporated in the model for women in preference over the data from Roberts *et al.*[209] The excess rates in men were estimated by applying the ratio of raw events observed between men and women from Roberts *et al.*[209] to the excess rates for women from Van Staa *et al.*[158]

The excess mortality rates attributable to hip fracture which have been applied in the model are presented in Table 18. In the PSA, these rates have been varied by estimating the numbers in each category in the patient cohort used by Van Staa et al[158] by assuming that the age distribution is similar to that of the general population[176] and using the estimated number with and without excess mortality to inform a beta distribution for each age band. The ratio of excess mortality rates for males versus females was not varied in the PSA.

Table 18: Excess mortality rates attributable to hip fracture

Age band	**Data for Women[158]**	**Ratio of rates (Male/Female)[209]**	**Estimate for Males**
50-59	2.4%	1.63[a]	3.9%
60-69	4.4%	1.63[a]	7.2%
70-79	7.5%	1.75	13.1%
80-89	11.4%	1.58	18.1%
90+	13.6%	1.47	20.0%

[a] assumed equivalent to ratio to that reported for ages 65-70

Abrahamsen et al report that around half of all mortality associated with hip fracture occurred within 3 months and 70% occurred by 6 months.[198] Given that Tosteston *et al.*[201] reported no excess mortality after 6 months following adjustment for a variety of factors, including pre-fracture functional status and comorbid conditions, we decided to assume that all deaths related to hip fracture occurred at exactly 3 months. A sensitivity analysis was conducted examining the alternative assumption that all deaths related to hip fracture occurred at exactly 1 month post fracture. Hip fractures occurring before age 50 were assumed not to result in any excess mortality.

A systematic review by Smith *et al.*[174] found that the relative risk of death following hip fracture for those residing at home compared with those residing in an institution prior to hip fracture was 0.57 (95%CI 0.43 to 0.72) when meta-analysed across 5 studies including a total of 25,497 participants. To reflect the increased risk of mortality for those institutionalised prior to hip fracture, we applied a relative risk of 1.75 (1/0.57) to the figures in Table 18 for those residing in institutional care prior to hip fracture. This may have slightly over-estimated the risk of mortality following hip fracture as some of the patients included in the study by van Staa *et al.*[158] will have been institutionalised and therefore the risks for non-institutionalised patients should be adjusted down. However, van Staa *et al.*[158] does not report the proportion institutionalised by age category within their sample so this adjustment was not possible. The likely bias introduced by not adjusting these figures is expected to be small as the majority of patients within the model do not reside in institutional care (see Figure 76 section 6.2.1.2).

6.2.1.11 Mortality after vertebral fracture

All of the papers included in the review of published cost-effectiveness analyses included some estimate of mortality following vertebral fracture within their economic evaluation. These papers were examined to determine the source data used.

The cost-effectiveness analysis by Van Staa *et al.* used estimates of mortality following clinical vertebral fracture which were derived by the authors themselves from a UK cohort of post-menopausal women identified from a database of general practice patients (GPRD).[158] The methods used in this paper to estimate mortality after vertebral fracture were the same as those used to estimate mortality after hip fracture and have been described above in section 6.2.1.9. Excess mortality rates are presented in this paper by age band but are limited to women. As described previously in Section 6.1 of this assessment report a second paper by van Staa *et al.*[160] used a similar method to estimate excess mortality after fracture in a cohort of UK patients treated with steroids but mortality rates were not reported in this second paper.

Two of the included cost-effectiveness papers[154,156] reported using estimates from Oden et al[212] but the absolute mortality rates could not be identified from the cited paper. Kanis *et al.*[159] (2007) cited seven studies[211,213-218] that provide data on the mortality risk after vertebral fracture. The only study to use a UK cohort, Jalava *et al.*,[216] examined the impact of prevalent and incident vertebral fractures on mortality rates in patients enrolled in a randomised control trial of clodronate. Jalava *et al.* commented that the small size of this study's cohort limited its ability to detect a mortality effect related to incident fractures with only 7 deaths occurring in patients with incident vertebral fractures.[216] Kanis *et al.* (2007)[159] used the relative risk associated with prevalent vertebral fractures from the UK study by Jalava *et al.* to determine the rate of deaths associated with vertebral fractures in their cost-effectiveness model.[216] Data from a Swedish study by Kanis *et al.* (2004) [218] were used by Kanis *et al.* (2007)[159] to determine the proportion of deaths (28%) that were causally related to vertebral fracture and data from a second Swedish study by Johnell *et al.*[211] were used to justify applying the same relative risk for males and females. Kanis et al (2004) provides estimates of the absolute risk of mortality stratified by gender and age bands and adjusts this to account for the proportion of deaths that are causally related.[218] Johnell *et al.* provides estimates of excess absolute risks by gender for ages 60 and 80 year by comparing the mortality rate in those with fractures against age and gender matched general population controls.[211] The remaining studies cited by Kanis et al (2007) did not provide estimates of absolute risk stratified by age and gender. No additional studies were identified from the cost-effectiveness studies by Kanis *et al.*, (2008) Borgstrom *et al.*(2006) and Stevenson *et al.* (2005).[155,157,163]

It should be noted that not all of the studies identified agreed about the causal nature of the relationship between vertebral fractures and mortality. Several studies found no statistically significant increase in mortality rates for incident fractures after adjusting for potential confounding factors.[216,219] Those studies which found a significant relationship[211,214,215,218] often did not adjust for potential confounding factors other than age and gender although Cauley *et al.*[213] did find a significant increase after adjusting for 6 comorbidities and pre-fracture health status.

Differences between findings across studies may also be related to whether they considered morphometric vertebral fractures or only those coming to clinical attention, which are likely to be more severe. The study by Kanis et al (2004)[218] considered only hospitalised vertebral fractures which could be expected to be more severe and associated with a higher death rate than non-hospitalised clinical vertebral fractures.

Some studies used baseline radiographs to confirm that the incident fracture was in fact new and not an undiagnosed prevalent fracture[213,219] but many studies[214,215,218] assumed that fractures which came to clinical attention had occurred recently. Kado *et al.*[217] (1999) considered only the impact of prevalent vertebral fractures with incident fractures for the same cohort considered in a later publication by Kado *et al.* (2003)[219].Those studies that considered morphometric fractures may also be complicated by the potential for delay between the fracture and the time it is found on radiograph. Kado *et al.* (2003), [219] whose study relied on a single radiograph during the follow-up period to identify incident morphometric fractures, noted that some fractures may have occurred between the last radiograph and the end of follow-up, with those patients being allocated to the no fracture group.

The data reported by van Staa *et al.*[158] were used in the model as this study used a large UK cohort, adjusted for multiple confounding factors and reported the excess risk for incident clinically symptomatic vertebral fractures. Although Center *et al.*[214] reported higher standardised mortality rates for men than for women when considering all vertebral fractures, the differences were small when considering incident vertebral fractures alone (1.6, 95%CI 1.4 to 1.8, in women *vs.* 1.8, 95%CI 1.6 to 2.0, in men). Johnell *et al.*[211] reported a non-significant trend for a higher relative risk in men than women and Kanis *et al.*[218] (2004) noted that the difference was not marked after taking into account of gender differences in mortality within the general population. Therefore we used the excess rates for women from van Staa *et al.*[158] and applied these to both men and women within our model. The timing of excess mortality attributable to vertebral fracture was less well discussed in the identified studies than for similar data for hip fracture. However, a graph of death hazard over time for both hip and vertebral fractures, presented by Kanis *et al.*,[218] suggests that a similar temporal pattern is seen for hip and vertebral fracture with high excess mortality in the early months. Therefore we assumed that all mortality related to vertebral fracture occurred at 3 months as this was the assumption used for hip fracture related mortality.

The excess rates following vertebral fracture applied in the model are presented in Table 19.

In the PSA the parameter uncertainty around these excess mortality rates has been calculated using the same method used for excess mortality following hip fracture (see section 6.2.1.10).

Table 19: Excess mortality rates following vertebral fracture

Age band	Excess mortality due to vertebral fracture
50-59	2.3%
60-69	3.5%
70-79	5.2%
80-89	6.7%
90+	6.6%

From van Staa *et al.* [158]

6.2.1.12 Excess mortality risk at fracture sites other than hip or vertebrae

Three of the seven papers included in our review of published cost-effectiveness analyses included an increased mortality risk for fractures at the proximal humerus.[157,159,160] Two of these studies[157,159] cited the paper by Johnell *et al.*[211] which found an increased risk of mortality compared with age and gender specific general population estimates, for patients with shoulder fracture, although the increase was not statistically significant at all ages. The third paper by van Staa *et al.*[160] used Cox-proportional hazards models to assess the excess mortality in the year following for hip, wrist, vertebral and proximal humerus fractures compared with age and gender matched controls in a population treated with steroids. These 1 year excess risks were incorporated in their analysis for all four fracture sites but no data on the excess risks are presented in their paper. In a similar analysis, van Staa *et al.*[158] examined the excess mortality associated with hip, wrist, vertebral and proximal humerus fracture, in a UK population of post-menopausal women. However they found that the excess risk of mortality was small for fracture types other than hip or vertebral fracture and didn't include any estimates of excess mortality for wrist or proximal humerus fractures in their analysis in postmenopausal women. A study by Cauley *et al.*[213] which analysed mortality rates pre and post fracture using data from an RCT, found no increased risk of mortality for fractures at sites other than the hip or vertebrae after adjusting for 6 comorbidities and pre-fracture health status. However, a more recent paper by Piirtola et al[220] found that the excess mortality rates following proximal humerus fractures were significantly increased in men but not women. Given that the evidence for an excess risk of mortality following proximal humerus fracture is not consistent across the studies we examined, we have not included any increased mortality risk for proximal humerus fractures.

Only one (van Staa *et al.*) of the published cost-effectiveness analyses, included in our literature review incorporated an increased risk of mortality for wrist fractures.[160] This paper

used estimates derived by the authors from a general practice database for a cohort treated with steroids, but estimates of the excess mortality by fracture type were not provided in the paper.[160] However two of the published analyses[157,159] stated that their assumption of no increased mortality risk following wrist fractures was consistent with published surveys.[211,213-215] We have assumed no increased risk of mortality following wrist fracture in our analysis.

Stevenson *et al.* and Kanis *et al.* (2007) grouped fractures occurring at sites other than the hip, wrist, proximal humerus and vertebrae into one of these four fracture types.[157,159] This meant that the excess mortality of hip fracture was also attributed to femoral shaft and pelvic fracture, and the excess mortality for proximal humerus fractures was also attributed to fractures of the humeral shaft, tibia and fibula. In our model, we have grouped other femoral fractures, but not pelvic fractures with hip fractures so that the excess mortality risk associated with hip fracture is also applied to other femoral fractures. The data we have used on excess mortality following hip fracture were taken from the paper by van Staa *et al.*[158] which also grouped other femoral factures with hip fractures and therefore the data are being used in a manner consistent with that which they were intended for. In summary, our analysis allows for excess mortality following fractures at the hip, femoral shaft or vertebrae but not for any other fracture site.

6.2.1.13 Risk of nursing home admission following hip fracture

Pain, reduced physical function and lack of mobility are common outcomes after hip fracture and can lead a patient who was previously living independently to require long-term nursing care. All of the published cost-effectiveness studies included in our review appeared to include some estimate of nursing home admission within their model. Two studies[155,156] included in the review of published cost-effectiveness analyses cited a conference poster by Zethraeus *et al.*[221] which gives the proportion of patients going into long-term care in the year following hip fracture surgery in Sweden by age band. Two of the published studies[157,159] used unpublished data from the East Anglian hip audit.[222] Three of the studies included in the review of published cost-effectiveness analyses [154,158,160] cited a report describing the model which was later published by Stevenson al.[157] as their source of data on nursing home admission following hip fracture, suggesting that they too applied the data from the East Anglian hip audit.

As the only UK data identified from the published cost-effectiveness analyses were unpublished data from a 1999 research report[222], more recent data were sought to inform the risk within the model of patients moving from living in their own home to nursing-home care after hip fracture. Age and gender specific data were sought as it was believed that there may

be a differential risk according to the age and gender of the patient. A scoping search identified a small number of papers addressing the issue of nursing home admission after hip fracture, of which four contained data on risk of discharge by both age and gender (Osnes *et al.*,[175] Holt *et al.*,[223] Deakin *et al.*,[224] Nanjayan *et al.*[225] These papers are summarised in Table 20.

The study by Holt *et al.*[223] despite covering a large sample in a UK population, was excluded on the basis that the analysis by age included only two age groups with relatively wide bounds (50-64 years and 75-89 years) and excluded patients aged 65-74 years. This was thought inadequate to assess the increasing risk of nursing home discharge with age.

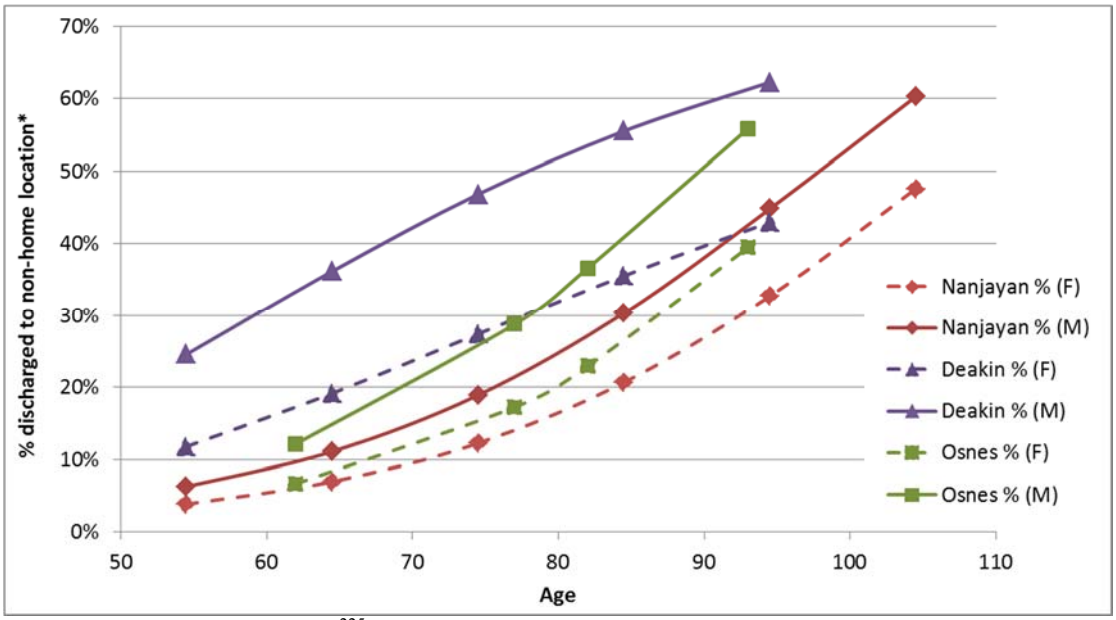
We calculated approximate age and gender specific probabilities for discharge to a non-home location using the overall probability of discharge to institutional care and odds ratios for age and gender reported by the remaining three studies. Studies by Osnes et al[175] and Nanjayan et al[225] gave similar results, but Osnes was thought less appropriate to the UK setting due to the potential for differences in social care structure and cultural norms regarding institutional care between the UK and Norway. Of the two UK studies, Nanjayan et al[225] was preferred, because the analysis explicitly excluded those who had died before discharge and was based solely on patients who were living in their own home prior to the fracture. Both of these criteria matched the model requirements, and hence data from Nanjayan *et al.*[225] were used in preference to those from Deakin *et al.* (Figure 92)

Table 20: Summary of studies identified reporting risk of discharge to nursing home care after hip fracture by age and sex.

Authors	Location	Patient group	Observation period	Method	Outcome measure	Variables of interest
Osnes et al, 2004[175]	Norway	Hip fracture patients aged 50+, excluding cancers N=593 living respondents (235 died, 174 non-responses)	184-584 days	Logistic regression	Discharge to nursing home	Age group: 50-74 years 75-79 years 80-84 years 85+ years And Male/Female
Holt et al, 2008[223]	Scotland	Hip fracture patients aged 50-89, excluding ages 90+, or without surgery N=17,357 living patients (3,085 lost to follow up)	120 days	Logistic regression	Residence at 120 days	Age group: 50-64 years 75-89 years And Male/Female
Deakin et al, 2008[224]	England	Hip fracture patients aged 50+, excluding bilateral, peri-prosthetic, road accident and pathological fractures. N= 3,240	Not stated (time to discharge)	Logistic regression	Discharge to an alternative location (to normal residence)	Age group: 50-59 years 60-69 years 70-79 years 80-89 years 90+ years And Male/Female

Authors	Location	Patient group	Observation period	Method	Outcome measure	Variables of interest
Nanjayan et al, 2014[225]	England	Hip fracture patients aged 50+, admitted from home, excluding no surgery. N= 1,503 (133 died)	Not stated (time to discharge)	Logistic regression	Discharge to an alternative location (to home)	Age group: 50-59 years 60-69 years 70-79 years 80-89 years 90-99 years 100+ years And Male/Female

Figure 92: Comparison of calculated discharge to non-home location rate by age for two UK (Nanjayan, Deakin) and one Norwegian (Osnes) study.



Values based on Nanjayan et al[225], F, females; M, males
*calculated based on odds ratios reported in the studies.

The overall rate of discharge to a non-home location (residential home, nursing home or hospitalisation) was given as 20% by Nanjayan *et al.*[225] Combining this with the known gender split of the cohort (71% female) and the stated odds ratios for each age and gender group, it was possible to derive an expected risk of non-home discharge for each age and gender group for use in the model; these are shown in Table 21. The risk of being discharged to a non-home location increases with increasing age (odds ratio 9.09 for patients aged

between 90 and 99 where odds ratio = 1 for patients of approximately 69 years) and is higher for males than females (odds ratio 1.67).

The risks of new admission to an institutional residential setting after hip fracture, presented in Table 21, have been applied within the model. In the PSA, these have been varied by applying a beta distribution to the overall rate of admission to an institutional residential setting on which the rates in the individual age and gender categories is dependent (see Appendix 9 for details on PSA distributions).

Table 21: Rate of new admission to an institutional residential setting, calculated from age- and gender-specific odds ratios.

	Odds ratio*		% Discharged from hospital to a non-home location, by age group	
Age band (years)			Female	Male
50-59	0.76		4%	6%
60-69	1.92		7%	11%
70-79	1.96		12%	19%
80-89	4.54		21%	30%
90-99	9.09		33%	45%
Female	1			
Male	1.67			
*from Nanjayan et al, 2014[225]				

6.1.2.13 Risk of nursing home admission following hip fracture

Only one of the papers included in our review of published cost-effectiveness analyses included a rate of nursing home admission following vertebral fracture. Kanis *et al.*[159] incorporated data on the rate of nursing home admission in Swedish patients from a paper by Borgstrom *et al.*[226] which reported similar rates of patients living in 'special living accommodation' for hip and vertebral fracture. However Borgstrom *et al.* [226] also noted in their discussion that their patient sample had a higher proportion than expected being hospitalised (72% versus expected 10%). The study by Borgstrom *et al.* [226] recruited patients at the time of fracture and no comparison was made to matched controls to remove costs that may be related to comorbidities. In comparison, a study by de Laet *et al.*[227] which did compare costs against matched controls found substantially higher costs of nursing home in hip fracture patients compared with controls but only small and non-significantly increased costs for vertebral fracture patients. However, this analysis conducted as part of the

Rotterdam Study, included patients with a new morphometric fractures and may therefore underestimate resource use in those with clinically apparent vertebral fractures. Given the lack of consensus on the incorporation of nursing home admission rates within the published analyses and the differing data from these two studies, we decided to omit nursing home admission following vertebral fracture from our basecase model but examine the impact of including a rate equivalent to that seen in hip fracture in a sensitivity analysis.

6.1.2.14 Risk of subsequent fracture after incident fracture

A systematic review and meta-analysis by Klotzbuecher *et al.*[228] has previously been used in several published economic evaluations to estimate the increased risk of fracture at various sites when a patient sustains an incident fracture within the model.[156,157,159] We conducted a citation search, using the Web of Science database, to find relevant articles published since the review by Klotzbuecher *et al.* on the assumption that new studies in this area would be likely to cite this published systematic review. We found 811 records of articles citing this systematic review. Given the large number of potentially relevant articles identified we tried to establish whether any more recent systematic reviews had been published. The abstracts and titles of these articles were then searched separately using the free-text terms 'review', 'meta-analysis' and 'synthesis' to see if any of these articles provided an updated systematic review and meta-analysis similar to that presented by Klotzbuecher *et al.*[228] Two potential systematic reviews were identified and full-texts examined. The first, by Haentjens *et al.*[229] was specifically interested in comparing whether the relative risk of hip fracture after a wrist or spine fracture differed by gender. Due to its focus on gender differences, this study had narrower inclusion criteria and excluded many of the studies included by Klotzbuecher *et al.*[228] and it only included one additional recent study.

The second systematic review identified from our citation search, which was authored by Blank (on behalf of the FRAX Position Development Conference Members),[230] identified around 20 studies published since the Klotzbuecher review. However, these studies are discussed narratively by Blank and no meta-analysis is provided.[230] It was not considered feasible to review and meta-analyse all of these new studies in order to update the estimates provided by Klotzbuecher *et al.*

A more recent review by Warriner *et al.*[231] which meta-analysed data from 25 studies published since the Klotzbuecher review, was identified opportunistically. The review by Warriner *et al.* does not provide any details regarding the methods used to identify the studies.[231] It also provides limited details on the studies included and does not tabulate the relative risks from the individual studies prior to pooling. It was therefore decided that the

estimates from Warriner *et al.* should be treated with caution due to the potential for selection bias. The estimates provided by Klotzbuecher *et al.*[228] were used in the base case model. These estimates were supplemented by data from Warriner *et al.*[231] where no estimates were provided by Klotzbuecher *et al.*[228] Neither meta-analysis provided data on the increased risks of fracture following proximal humerus fracture. Data on the increased risk following fracture at any site were used as a proxy for risk following fractures at the proximal humerus. Neither meta-analysis provided data on the risk of proximal humerus facture after hip fracture so the data on proximal humerus fracture following fracture at any site from Warriner was used. The data in Table 22 were applied in the model as hazard ratios within the survival curves used to estimate time to fracture for the basecase analysis. A sensitivity analysis has also been conducted using the estimates from Warriner *et al.* [231] exclusively, which are shown in Table 23.

The values from Klotzbuecher[228] and Warriner[231] are applied for the patient's remaining lifetime once a fracture occurs. The studies included by Klotzbuecher *et al.* in the meta-analysis had varying durations of follow-up but were generally greater than 1 year so the estimates provided by Klotzbuecher represent the relative risk when averaged over all years of study follow-up. The temporal profile of increased fracture risk after an incident fracture has been studied by van Geel *et al.*[232] Their analysis suggests that the RR is approximately 2 when averaged over the long-term but when the RR is assessed over different time periods there is a much higher relative risk immediately after the first facture which tails off towards 1 over the next 20 years. We acknowledge that our method of applying a fixed relative risk over the patients' remaining life-time probably underestimates the increased risk in the immediate years after fracture but is likely to overestimate the increased risk in the long-term. The alternative would be to use additional dummy events to modify the increased risk in the years after fracture but this would reduce the computational efficiency of the model. In the PSA, the hazard ratios in Table 22 were sampled from a lognormal distribution using SEs calculated from the 95%CIs reported in Table 22 (see Appendix 9 for PSA distributions).

When more than one incident fracture was sampled to occur during a patient's lifetime, the maximum value from Table 22 has been applied for each subsequent fracture type rather than applying several multipliers concurrently. For example if someone has had a prior wrist fracture and a prior vertebral fracture then their increased risk of vertebral fracture is 4.4 which relates to their prior history of vertebral fracture as this is the maximum value in the vertebral column in Table 22. However, their increased risk for proximal humerus fracture would be 2.5 which relates to their prior history of wrist fracture as this is the maximum value in the proximal humerus column.

Both QFracture and FRAX incorporate an increased risk for patients with a history of prior fracture and therefore those with a prior fracture at the start of the model already have an increased risk applied for prevalent fractures. This increased risk associated with fractures occurring prior to the start of the model is removed at the time of the first incident fracture and the data from Table 23 are applied instead. This is to prevent the risk being increased twice for the same patient characteristic using two different mechanisms within the model.

Table 22: Increased risk of subsequent fracture following incident fracture

	Site of subsequent fracture			
Location of prior fracture	**Wrist**	**Vertebral**	**Hip**	**Proximal humerus**
Wrist	3.3 (2.0 to 5.3) [a]	1.7 (1.4 to 2.1) [a]	1.9 (1.6 to 2.2) [a]	2.5 (0.6 to 10.2)[b]
Vertebral	1.4 (1.2 to 1.7) [a]	4.4 (3.6 to 5.4) [a]	2.3 (2.0 to 2.8) [a]	1.6 (0.7 to 3.0)[b]
Hip	3.0 (1.3 to 6.5)[b]	2.5 (1.8 to 3.5) [a]	2.3 (1.5 to 3.7) [a]	2.1 (0.3 to 17.3) [a]
Proximal humerus[c]	1.9 (1.3 to 2.8)[a]	2.0 (1.6 to 2.4)[a]	2.0 (1.9 to 2.2)[a]	2.1 (0.3 to 17.3)[b]

[a]Data from peri/postmenopausal women from Table 1 of Klotzbuecher

[b]Data from Warriner applied as no data available from Klotzbuecher.

[c]Data from prior fracture at any site used when site specific data not available

Table 23: Increased risk of subsequent fracture following incident fracture used in sensitivity analysis

	Site of subsequent fracture			
Location of prior fracture	**Wrist**	**Vertebral**	**Hip**	**Proximal humerus**
Wrist	3.2 (1.3 to 8.1)	2.9 (1.6 to 5.3)	2.9 (2.0 to 4.1)	2.5 (0.6 to 10.2)
Vertebral	1.8 (1.1 to 3.2)	4.9 (2.4 to 9.8)	3.7 (2.3 to 5.9)	1.6 (0.7 to 3.0)
Hip	3.0 (1.3 to 6.5)	3.6 (1.9 to 6.7)	3.7 (2.5 to 5.3)	2.1 (0.3 to 17.3)
Proximal humerus[c]	2.6 (1.8 to 3.8)	3.0 (2.2 to 4.0)	2.4 (1.6 to 3.5)	2.1 (0.3 to 17.3)

[a]Data from peri/postmenopausal women from Table 1 of Klotzbuecher

[b]Data from Warriner applied as no data available from Klotzbuecher.

[c]Data from prior fracture at any site used when site specific data not available

6.2.1.15 Health-related quality of life: review of utility values following fracture

To inform the model, data was needed on the proportionate decrease in health-related quality of life (HRQoL) that occurs in the year following fracture and in subsequent years. This was then used to calculate a utility multiplier which was applied to the pre-fracture utility value to calculate the post-fracture utility. For example a proportionate decrease of 10% would translate into a utility multiplier of 0.9. If the patient's prior fracture utility is 0.8 then the post fracture utility would be 0.72. Data on the absolute HRQoL after fracture can be obtained from studies which measure HRQoL in patients who have experienced a recent fracture. However, the proportionate decrease can only be obtained if there is some estimate of pre-fracture utility. Ideally HRQoL would be measured prospectively in a cohort of patients at risk of fracture and these patients would be followed up with HRQoL re-measured at regular intervals with the time of any incident fracture being recorded so that the correlation between HRQoL and incident fracture can be obtained after adjusting for other confounding factors. However, many studies simply recruit patients at the time of fracture and ask them to recall their pre-fracture health state which is subject to recall bias. Other studies may compare the HRQoL in individuals who have fractured with matched controls or population norms, in which case the estimates may be confounded by differences in other factors between cases and controls.

Initially a systematic search was conducted to identify studies reporting any measure of health utility in patients with an incident osteoporotic fracture. However this search retrieved 3,991 unique references and it wasn't considered feasible to sift such a large number of papers within the timescales of the NICE appraisal process. As the NICE methods guide[161]tates that EQ-5D is the preferred measure of health-related quality of life in adults, and a recent systematic review by Peasgood et al[233] had already demonstrated that EQ-5D data exist for the four major osteoporotic fracture sites, the search was made more specific with the aim of identifying only those studies reporting HRQoL data measured using the EQ-5D. This more sensitive search retrieved 132 references and sifted for relevant papers.

Studies reporting HRQoL values measured during RCTs were excluded due to the possibility that study interventions may affect HRQoL independently of their impact of fracture. In addition studies which examined the HRQoL impact of surgical interventions to treat fracture were excluded as these were focused on comparing the impact of different surgical techniques on quality of life rather than comparing pre and post-fracture HRQoL under usual management. Studies reporting the quality of life impact of prevalent fractures were excluded on the basis that there is no way of knowing how long ago the prevalent fracture was

sustained and the model requires information on the quality of life impact in the year following fracture and in subsequent years.

Sixteen studies remained (summarised in Table 24) of which 8 provided HRQoL for hip fractures, 8 for wrist fractures, 10 for vertebral fractures and 3 for shoulder fractures. Of these, two studies used non-UK utility values (Hagino 2009)[234] and (Calvo 2011)[235] and two were of very specific patient cohorts making the results of these studies less relevant to the general population at risk of fragility fracture. Cooper et al (2008)[236] focused on women with inadequate response to therapy and Ekstrom et al (2009)[237] focused on patients with sub-trochanteric hip fractures only. Therefore HRQoL values from these studies were not considered further.

Four studies did not provide a pre-fracture or control utility value and these were excluded except where no other values were available (Zethraeus *et al.*[238] Dolan *et al.*,[239], Suzuki *et al.*[240] and Suzuki *et al.*[241]).

Five of the included papers contained duplicate results, since both papers by Tidermark et al,[242,243] referred to the same study and the papers by Strom *et al.*[244] and Borgstrom *et al.*[245] referred to a single study (known as KOFOR). The later paper by Borgstrom *et al.*[245] was an international extension to the KOFOR study (known as ICUROS) which gave HRQoL values by country but not pooled. The Swedish cohort within ICUROS appeared to have been based on a slightly expanded version of the KOFOR sample. Of the ICUROS results, the Swedish values were thought to be the most appropriate because they were based on the largest sample of the various country-specific cohorts and they were expected to provide a good estimator of UK HRQoL values, since Northern European countries have been shown to have similar values (Van Schoor 2008).[246]

Table 24: Summary of included papers reporting EQ-5D quality of life measures associated with osteoporotic fracture

First author, year	Country	Study design	Cohort description	Sample size at baseline and % missing data	Valuation set used for EQ-5D	Reasons for not considering some studies further
Hagino *et al.*, 2009[234]	Japan	Prospective cohort	Patients aged 45 years or over with osteoporotic hip, wrist or spine fracture.	Recruited: 122 13% dropped out, excluded due to additional fractures or death	Japanese health utility rating	Not used because not UK TTO
Cooper *et al.*, 2007[236]	Europe	Prospective cohort (OSSO)	PM women with osteoporosis and inadequate response to therapy	Recruited: 166 with incident fracture	UK scoring algorithm	Not used, study is with specific cohort of women with inadequate response to therapy
Ekstrom *et al.*, 2009[237]	Sweden	Prospective cohort	Patients with sub-trochanteric hip fracture treated with cephalomedullary nail	Recruited: 87 Missing: 4 months: 11% 12 months: 21% 24 months: 38%	UK TTO	Not used, study is with patients with sub-trochanteric hip fracture which make up a small percentage of all hip fractures
Calvo *et al.*,2011[235]	Spain	Prospective cohort	PM women aged >50 (acute, outpatient, non-operative osteoporotic fractures only)	Recruited with HRQoL: 301 Overall: 5,506 (6.5% dropped out, 6.7% excluded) HRQoL n =	Spanish EQ-5D	Not used because not UK TTO
Zethraeus, 2002[238]	Sweden	Prospective cohort, pilot	Patients aged 50 years and over with hip, spine, wrist or shoulder fractures recruited at the orthopaedic department	Recruited (response rate at 2 weeks) Hip:533 (18%) Shoulder:210 (25%) Wrist:334 (42%) Spine: 172 (25%)	UK Tariff	No pre-fracture or control value reported. Used only where no other data available

First author, year	Country	Study design	Cohort description	Sample size at baseline and % missing data	Valuation set used for EQ-5D	Reasons for not considering some studies further
Suzuki *et al.*, 2008[240]	Sweden	Prospective cohort	Patients over 40 years with acute osteoporotic spine fracture	Recruited 147 27% lost to follow up, died or excluded	UK TTO	Not used because no pre-fracture or control value reported
Suzuki *et al.*, 2010[241]	Sweden	Prospective cohort	Patients over 40 years with acute osteoporotic spine fracture with or without prevalent fracture	Recruited 56 with no prevalent fracture	UK TTO	Not used because no pre-fracture or control value reported
Dolan *et al.*, 1999[239]	UK	Prospective cohort	Women with wrist fracture	Recruited: 50	UK TTO	Not used because no pre-fracture or control value reported
Tidermark *et al.*, 2002[242]	Sweden	Prospective cohort	Patients 65+ years with acute hip fracture and internal fixation	Recruited 90 33% died, excluded or lost to follow-up by 24 months	UK TTO	Considered relevant
Tidermark *et al.*, 2002[243]	Sweden	Prospective cohort	Patients 65+ years with acute hip fracture and internal fixation	Recruited 90 28% excluded, lost to follow-up or underwent different surgery	UK TTO	Considered relevant
Strom *et al.*, 2008[244]	Sweden	Prospective cohort (KOFOR)	Patients 50+ with a single osteoporotic fracture of hip, spine or wrist	684 patients survived to 18 month follow-up	UK TTO	Considered relevant and applied in model
Borgstrom *et al.*, 2006[226]	Sweden	Prospective cohort (KOFOR)	Patients 50+ with a single osteoporotic fracture of hip, spine or wrist	Recruited 635 1% excluded	UK TTO	Considered relevant

First author, year	Country	Study design	Cohort description	Sample size at baseline and % missing data	Valuation set used for EQ-5D	Reasons for not considering some studies further
Borgstrom *et al.*, 2013[245]	International (11 countries including UK)	Prospective cohort (ICUROS)	As KOFOR, patients within 2 (6 in US) weeks of fracture.	2,808 analysed using combined dataset with KOFOR study. Results presented by country, UK not reported.	UK TTO	Considered relevant
Lips *et al.*, 2010[247]	Europe (5 centres including UK)	Prospective cohort	Ambulant patients aged 45-80 years within 14 days of wrist fracture and age/sex matched controls	Recruited: 105 + 74 controls 13% drop out,	Unclear	Considered relevant
Roux *et al.*, 2012[248]	International (10 countries including UK)	Large prospective cohort (GLOW)	PM Women with osteoporosis followed up for spine, hip and other fractures	Recruited: 1,822 fractures from 51,491 women	Country-specific utilities.	Considered relevant
Cockerill *et al.*, 2004[249]	Europe (7 countries including UK)	Population-based screening survey case-control follow-up (EVOS)	Men and women 50-79 years screened for spine fracture	Recruited: 121 fractures with HRQoL from 15,570 people screened	UK TTO	Considered relevant

HRQoL = health-related quality of life, TTO = time trade-off

Values from eight papers reporting outcomes from five distinct studies were therefore compared. All studies appeared to observe similar patterns in HRQoL, with an immediate, severe drop in HRQoL associated with the acute fracture incident (where recorded), followed by a recovery to a higher HRQoL within the first four months, and stabilisation or slow improvement over the course of the year to twelve months. The exception to this was the Roux *et al.*[248] study which was a prospective study where utility was measured at enrolment (pre-fracture) and then after twelve months, with the post-fracture values being twelve-month values for patients who experienced a fracture at any time during the previous twelve months. As a result values from the Roux study showed a gradual decline over a twelve-month period. The advantage of this approach is that pre-fracture utilities were as measured and therefore not subject to recall bias. Twelve-month values should also theoretically represent an average of utility loss associated with fracture over a year, assuming all patients were surveyed at exactly twelve months. However, since a significant amount of utility loss is experienced in the first days and weeks after fracture, the results could easily be biased if patients who had recently experienced a fracture delayed completing the survey. Since the study was based on self-completion postal questionnaires it was considered possible that there may be some reporting bias in this study, and therefore values from other studies were considered more appropriate. One of the papers by Tidermark *et al.*[243] did not report a HRQoL value between baseline and 4 months and therefore this study did not observe the severe drop in HRQoL associated with the acute fracture incident. A summary of the values reported by individual studies for utility after hip fracture, wrist fracture, vertebral fracture and shoulder fracture are presented in Table 25, Table 26, Table 27 and Table 28 respectively.

Values were plotted and a weighted average score was calculated for each fracture type. An example is shown in Figure 93 for hip fracture, for which five appropriate papers were sourced, relating to two studies. The weighted average score closely followed the result of the largest study (KOFOR/ICUROS) reported in the papers by Strom et al[244] and Borgstrom *et al.* [226] Similar patterns were observed for all fracture types. The KOFOR/ICUROS study was the only study to provide pre- and post-fracture values for hip, wrist and spine fractures. It also had the largest sample size and reported similar results to other studies. Therefore, the decision was made to use values from the KOFOR/ICUROS study as the basis of the utility multipliers applied in the model. No study provided complete HRQoL data for shoulder fracture, however, so in this case values from Zethraeus *et al.*,[238] were used, with an assumption that post-fracture HRQoL measured at 12 months represented a return to pre-fracture HRQoL levels. No studies reported pre-fracture (or control) and post-fracture values for fractures at sites other than the hip, wrist, spine or shoulder.

Table 25: Utility values after hip fracture

First author, year	Description of non-fracture state	Valuation of non-fracture state, Mean (sd, N)	Description of fracture states valued	Value of fracture states, Mean (sd, N)
Roux *et al.*, 2012[248]	Baseline pre-fracture	0.64 (0.34, 126)	0-12 months post-fracture (12 months post-recruitment)	0.60 (0.34, 126)
Strom *et al.*, 2008[244]	Pre-fracture (recalled)	0.81 (0.21, 282)	Post fracture at immediate: 4 months: 12 months: 18 months:	 0.19 (0.21, 282) 0.64 (0.26, 282) 0.69 (0.26, 282) 0.72 (0.26, 282)
Borgstrom *et al.*, 2013[245]	Pre-fracture (recalled)	0.80 (0.24, 355)	Post fracture Immediate: And 4 months	 0.18 (0.19, 355) 0.62 (0.24, 355)
Tidermark *et al.*, 2002[242]	Pre-fracture (recalled)	0.77 (NR, 90)	Post fracture at 4 months: 12 months: 24 months:	 0.66 (NR, 42) 0.62 (NR, 42) 0.59 (NR, 42)
Tidermark *et al.*, 2002[243]	Pre-fracture (recalled): and age-matched general population:	0.78 (0.21, 89)	Post fracture at 1 week: 4 months: 17 months:	 0.44 (0.33, 71) 0.55 (0.37, 79) 0.51 (0.36, 69)
Borgstrom *et al.*, 2006[226]	Pre-fracture (recalled)	0.80 (0.21 277)	Post fracture at 0-4 weeks: 4 months: 12 months:	 0.18 (0.21, 277) 0.62 (0.30 277) 0.67 (0.25, 277)

NR = not reported

Table 26: Utility values after wrist fracture

First author, year	Description of non-fracture state	Valuation of non-fracture state Mean (sd, N)	Description of fracture states valued	Value of fracture states Mean (sd, N)
Lips *et al.*, 2010[247]	Age/sex matched controls	0.85(median) (NR,73)	Post fracture 0-14 days (baseline): 6 weeks: 3 months: 6 months: 12 months:	Median 0.59 0.66 0.76 0.78 0.80
Strom *et al.*, 2008[244]	Pre-fracture	0.90 (0.18, 325)	Post fracture at immediate: 4 months: 12 months: 18 months:	 0.56 (0.28, 325) 0.83 (0.18, 325) 0.88 (0.23, 325) 0.90 (0.18, 325)
Borgstrom *et al.*, 2013[245]	Pre-fracture (recalled)	0.90 (0.20, 390)	Post fracture at immediate: 4 months:	 0.56 (0.25,390) 0.83 (0.20,390)
Borgstrom *et al.*, 2006[226]	Pre-fracture (recalled)	0.89 (0.17 276)	Post fracture at 0-4 weeks: 4 months : 12 months:	 0.56 (0.17, 276) 0.82 (0.17, 276) 0.86 (0.17, 276)

NR = not reported

Table 27: Utility values after vertebral fracture

First author, year	Description of non-fracture state	Valuation of non-fracture state	Description of fracture states valued	Value of fracture states Mean (sd, N)
Roux *et al.*, 2012[248]	Baseline pre-fracture	0.65 (0.02, 178)	0-12 months post-fracture (12 months post-recruitment)	0.58 (0.02, 178)
Strom *et al.*, 2008[244]	Pre-fracture	0.74 (0.24, 76)	Post fracture at immediate: 4 months: 12 months: 18 months:	 0.18 (0.27, 76) 0.49 (0.31, 76) 0.49 (0.31, 76) 0.54 (0.31, 76)
Borgstrom *et al.*, 2013[245]	Pre-fracture (recalled)	0.74 (0.25, 120)	Post fracture at immediate: 4 months:	 0.20 (0.28, 120) 0.50 (0.34, 120)
Borgstrom *et al.*, 2006[226]	Pre-fracture (recalled)	0.73 (0.25, 81)	Post fracture at 0-4 weeks: 4 months : 12 months:	 0.18 (0.25, 81) 0.47 (0.34, 81) 0.49 (0.25, 81)
Cockerill *et al.*, 2004[249]	Age/gender-matched controls: Prevalent fracture found: No prevalent fracture:	 0.81 (0.19, 60) 0.83 (0.17, 136)	Incident fracture cases:	0.77 (0.19, 73)

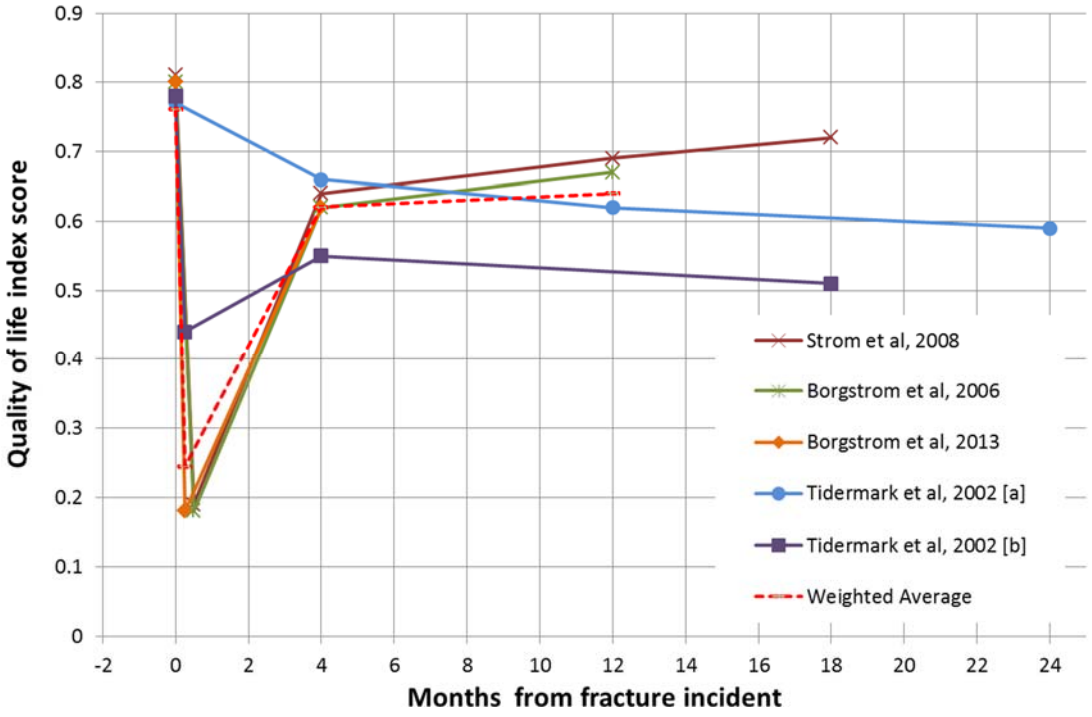
NR = not reported

Table 28: Utility values after shoulder fracture

First author, year	Description of non-fracture state	Valuation of non-fracture state	Description of fracture states valued	Value of fracture states Mean (sd, N)
Zethraeus, 2002[238]	None	NR	Post fracture at 2 weeks 6 months 9 months 12 months	 0.36 (sd 0.30, N=46) 0.69 (sd 0.25, N=40) 0.66 (sd 0.26, N=37) 0.65 (sd 0.29, N=30)

NR = not reported

Figure 93: Illustration of post-fracture trends in HRQoL taken from five papers reporting on two different studies plus a weighted average.



The average utility value in the first year following fracture has been calculated by assuming an immediate drop in HRQoL at fracture maintained for one month, followed by a linear improvement to four months and then a further linear improvement to 12 months. The utility multiplier applied in the first year post fracture was then calculated as the ratio of the average utility in the year post-fracture to the baseline utility prior to fracture. The utility value observed at 12 months is assumed to persist in the long-term so the multiplier for the second and subsequent years was set to the ratio of the 12 month and pre-fracture utility value.

The data applied in the model are summarised in Table 29. The post fracture utility values have been varied in the PSA by sampling values from a beta distribution (see Appendix 9 for details on the distributions).

Table 29: Calculation of utility multipliers from quality of life study results

		Hip*	Spine*	Shoulder**	Wrist*
Number of patients		282	76	38	325
Utility index	Pre-fracture	0.81	0.74	0.65***	0.90
	2 weeks post	0.19	0.18	0.36	0.56
	4 months post	0.64	0.49	0.58	0.83
	12 months post	0.69	0.49	0.65	0.88
	Annual average	0.56	0.43	0.56	0.79
Utility multiplier (year 1)		0.69	0.57	0.86	0.88
Utility multiplier (year 2 and subsequent)		0.85	0.66	1.00	0.98

*Strom et al, 2008[244]

**Zethraeus et al, 2002[238]

***assumed based on 12 months post-fracture value

6.2.1.16 Health-related quality of life values for institutionalisation

Tidermark *et al.* found that in a prospective cohort study of 90 patients with hip fracture, who were living independently prior to their fracture, patients with an independent living status after fracture had significantly better EQ-5Dindex scores than those living in institutions at 4 months (0.64 and 0.35, respectively, $p < 0.05$).[243] A similar difference in mean scores (0.56 versus 0.35) was seen at final follow-up (>12 months after fracture with mean follow-up of 17 months) but this was no longer statistically significant. The lack of statistical significance at final follow-up may be due to the small number of patients institutionalised (7 at 4 months and 8 at 17 months). We used the data from final follow-up within our analysis to calculate a utility multiplier for nursing home admission following fracture of 0.625. This is higher than the value of 0.4 used in four of the published analyses[157-160] However, this earlier value was based on judgement by an expert panel.[169] The remaining three published analyses didn't describe the utility multiplier applied for nursing home admission. The multiplier calculated from Tidermark *et al.* was used in our model as this was based on EQ-5D scores valued using the UK tariff which is consistent with the NICE reference case.[161] Tidermark *et al.* did not report standard deviations for the mean EQ-5D values for institutionalised patients and patients living independently. To provide an estimate of uncertainty in the utility multiplier within the PSA, the standard error around the utility multiplier was set to give a 95%CI that coincided with no difference between these two health states, to reflect the lack of a statistically significant difference in the mean values at 17 months.

6.2.1.17 Age and gender specific utility values in the absence of clinical events

Utility in patients without fracture is dependent on age and gender and is based on EQ-5D data for the UK general population.[250] The age and gender dependent utility value applied to the period between two events is taken to be the average of the utility at the start and end of that period. This ensures that patients who do not experience any events do not stay at an artificially high level of utility, equivalent to the utility value for their age at the start of the model. The regression used to calculate utility from age and gender is as follows:

Utility = 0.9508566 – 0.0212126 *gender -0.0002587*Age -0.0000332*Age*Age

where gender is 1 for males and 0 for females and age is in years.

A multivariate normal distribution which takes into account the correlation between the regression coefficients was used to sample the regression coefficients in the PSA.

6.2.18 Costs of fracture

Resource use attributable to fracture was based on a UK study by Gutierrez *et al.*[251,252] which used a GP database (The Health Improvement Network [THIN] database) to estimate resource use for those who fractured compared with matched controls. Patients were matched on age, GP practice and comorbidity score. The study was reported in two separate papers with the first reporting the costs attributable to hip fracture and the second reporting the costs attributable to vertebral fracture, non-hip non-vertebral fracture and also some less detailed results for wrist and proximal humerus fracture.[252] The study examined hospitalisations, accident and emergency (A&E) visits, referrals, prescriptions and GP contacts in the year following fracture. It didn't examine any costs falling within personal social services such as nursing home admission or home help. The authors also noted that they did not include rehabilitation costs but they did estimate the total cost including rehabilitation by using estimates of rehabilitation costs from other published studies.

The difference in the percentage of patients using each type of resource between those who had fractured and matched controls was multiplied by the unit cost to get the average cost per fracture in the year following fracture. Unit costs for hospitalisations, A&E appointments and specialist referrals were based on NHS reference costs while unit costs for social care and GP appointments were based on estimates from the PSSRU. Table 30 and Table 31 show the difference in resource use between patient who fractured and their matched controls and the unit costs applied. The total first year and subsequent year costs are summarised in Table 32. Unit costs for A&E vary by fracture type as different costs were applied for admitted and

non-admitted patients and these proportions vary by fracture type. Unit costs for prescriptions were calculated by dividing the difference in total prescription cost by the difference in the mean number of prescriptions using data from Gutierrez *et al.*[252] However this detailed information was not available for wrist and proximal humerus fractures so data from the broader category of non-hip non-vertebral fractures was used for wrist and proximal humerus.

In the cost-effectiveness analysis which informed TA160 and TA161[157] it was assumed that patients who experienced a vertebral fracture had on-going costs in the 2nd and subsequent years associated with the long-term prescribing of treatments to manage the chronic symptoms associated with vertebral fractures. The analysis by Gutierrez *et al.* doesn't examine costs beyond the first year, however, it can be seen that for both vertebral fracture, non-hip non-vertebral fractures, and hip fractures the costs of medications are fairly stable in the first and second 6 months following fracture whereas the costs for healthcare contacts such as GP appointments, referrals and A&E visits fall sharply in the second 6 months.[252] We therefore decided to apply prescription costs as an on-going cost from the time of fracture. All other costs estimated by Gutierrez were applied in the first year only.

In the analysis by Stevenson et al[157] Swedish data presented by Borgstrom et al[226] were used to estimate the costs of home-help. We used the same data on the average number of hours of home help following fracture as used by Stevenson *et al.* [157] but applied present day unit costs. Home help costs are assumed to occur only in the first year after fracture and only apply to those residing in the community and not to institutionalised patients.

For patients living in an institutional residential setting we applied the cost of Local Authority provided residential care for older people with the unit cost (£1,100 per week) taken from PSSRU.[27] The costs for Local Authority provided care were used instead of private sector or NHS residential care as a recent report by the King's Fund states that the vast majority (78%) of residential care places are provided by local authorities.[253] We assumed that 36% of patients self-fund their residential care based on data presented by the Care Quality Commission.[254] The annual cost falling within the NHS and PSS budget was therefore estimated at £36,608 per person in residential care per annum. In the PSA, both the resource use estimates in Table 30 and the unit costs taken from NHS reference costs were sampled from probabilistic distributions. Those taken from PSSRU were not varied in the PSA as PSSRU does not report a measure of variance. Further details on the distributions used in the PSA are provided in Appendix 9.

The costs for each of the four main osteoporotic fracture sites has been applied to other sites in the same grouping (e.g. other femoral has same cost as hip).

Table 30: Resource use attributable to fracture

	Difference in proportion between patients with fractures and controls			
Resource use	Hip	Vertebrae	Proximal humerus	Wrist
Hospitalisation	0.82	0.23	0.20	0.17
A&E	0.14	0.07	0.15	0.18
GP	-0.02	0.07	0.03	0.06
Referral	0.01	0.17	0.05	0.09
	Mean difference in number			
Prescriptions per annum	12.34	22.35	4.61	4.61
Home help hours per week[a]	1.57	2.33	0.12[b]	0.12

[a] home help hours are based on data from Borgstrom et al[226] which did not compare against matched controls and is therefore simply the mean number of hours in patients

[b] assumed equal to wrist

Table 31: Unit costs for resource use attributable to fracture

	Unit costs			
Resource use	**Hip**	**Vertebrae**	**Proximal humerus**	**Wrist**
Hospitalisation	£7,487	£3,846	£5,320	£3662
A&E	£92	£85	£85	£84
GP	£45	£45	£45	£45
Referral	£146	£146	£146	£146
Prescriptions	£9	£15	£15	£15
Home help per hour	£24	£24	£24	£24

Table 32: Summary of fracture costs in the year following fracture and in subsequent years

Resource use	Hip	Vertebrae	Proximal humerus	Wrist
Costs in year of fracture	£8,235	£4,173	£1305	£861
Costs in subsequent years	£106	£332	£70	£70

6.2.1.19 Resource use and costs for bisphosphonates treatment

Drug costs for oral bisphosphonates have been taken from the National Drug Tariff as these are assumed to be prescribed in primary care.[161,255] Zoledronate and i.v. ibandronate are assumed to be prescribed in secondary care and costs for these have therefore been taken from the eMIT database which reports the average cost paid by secondary care trusts for generic medicines.[42,161] It was noted by our clinical advisors that generic zoledronate has only recently become available and therefore the prices reported by the eMIT database may be higher than those currently being paid in the NHS as the price is likely to fall after a generic preparation becomes available and the current eMIT database uses data from the 12 months prior to June 2014. Therefore a sensitivity analysis was conducted using the price for the 4mg preparation of zoledronate which is for a different indication but has been available in generic form for a longer time. This was felt to represent a realistic lower limit for the price of the 5mg preparation.

Where there was more than one preparation available we have assumed that the lowest cost preparation is prescribed based on the average cost for 1 year of treatment. Therefore for alendronate and risedronate we assumed that weekly preparations are prescribed as these had the lowest costs based on the National Drug Tariff. Drug costs applied in the model are summarised inTable **33**. Drug prices are assumed to be known precisely and therefore have been assumed to be fixed within the PSA.

Table 33: Costs based on the National Drug Tariff

Bisphosphonate	Items per pack and dose per item	Price per pack	Cost per annum
Alendronate (oral)	4 x 70mg	£1.13[a]	£14.73

Risedronate (oral)	4 x 35mg	£1.26[a]	£16.43
Ibandronate (oral)	28 x 50mg	£10.56[a]	£13.58
Ibandronate (i.v.)	1 x 3mg / 3ml	£19.38[b]	£77.52
Zoledronate (i.v.)	1 x 5mg / 100ml	£94.67[b]	£94.67
Zoledronate (i.v.) (price used in sensitivity analysis)	1 x 4mg/5ml	£5.76[b]	£5.76

[a] National Drug Tariff

[b] eMIT database

Oral therapies were assumed to incur no additional costs for administration. The cost of i.v. administration of zoledronate and ibandronate have been based on NHS reference costs.[256] Ibandronate is given by i.v. injection over 15-30 seconds. It is assumed that this is done during an outpatient endocrinology consultation at a cost of £133 (NHS reference cost 302) [256]. Zoledronate is given by intravenous infusion over a longer duration and this is assumed to be done as a day case. The reference cost for a day case delivery of a simple parenteral chemotherapy (SB12Z at £245) [256] has been applied as no alternative reference costs were identified which would cover day case admissions for the administration of a drug by infusion. The outpatient cost for the same HRG code (SB12Z) is £165 suggesting that it is classification of this activity as a day case rather than the specific nature of chemotherapy that makes this more expensive than an outpatient endocrinology appointment. It was therefore considered reasonable to apply the day case reference cost for parenteral chemotherapy as a proxy for the cost of delivering zoledronate due to the longer duration of administration compared with i.v. ibandronate. Our clinical advisors noted that in some cases zoledronate is administered as an outpatient procedure and therefore a sensitivity analysis was conducted using the outpatient cost for both i.v. bisphosphonates. Reference costs for the administration of i.v. bisphosphonates were varied in the PSA (for details see Appendix 9).

6.1.1.20 Approach to sensitivity analysis

A probabilistic sensitivity analysis (PSA) has been conducted to estimate the mean cost and QALYs gained when taking into account the uncertainty in the parameter values used within the model. In general parameters were estimated using the following distributions; gamma distributions for costs; lognormal distributions for hazard ratios; beta distributions for utility values and probabilities. None of the parameters used to estimate fracture risk, in the absence of treatment, were varied in the PSA. This was to ensure that a specific set of patient characteristics was consistently mapped to the same survival curve for fracture-free survival without any parameter uncertainty. The following additional parameters were not varied in the PSA: drug prices; discount rates; unit costs sourced from PSSRU; utility in the second year after proximal humerus fracture; life-expectancy after fracture associated with excess mortality; unit costs for prescriptions after fracture; proportion of self-funders for residential care. Full details on the distributions applied within the model can be found in Appendix 9.

Structural sensitivity analyses were conducted to explore whether the results were sensitive to different models assumptions. These were conducted using the deterministic model which does not incorporate any parameter uncertainty due to the significant computational time required to run the PSA. The structural sensitivity analyses were conducted using the model assuming full persistence with treatment as this model required fewer patients to achieve stable results than the model which applies persistence data from observational studies.

6.2.2 Results

6.2.2.1 Characteristics of the simulated cohort

Summary characteristics are provided in Table 34 for each risk category when using both FRAX and QFracture to calculate the absolute fracture risk. It can be seen that the average age is higher in the higher risk categories and the proportion of patients with the risk factors of prior fracture, steroid use or nursing home residency increases in the higher risk categories. The proportion of women also appears to increase in the higher risk categories as would be expected given that women in general have a higher risk of osteoporotic fracture than men.

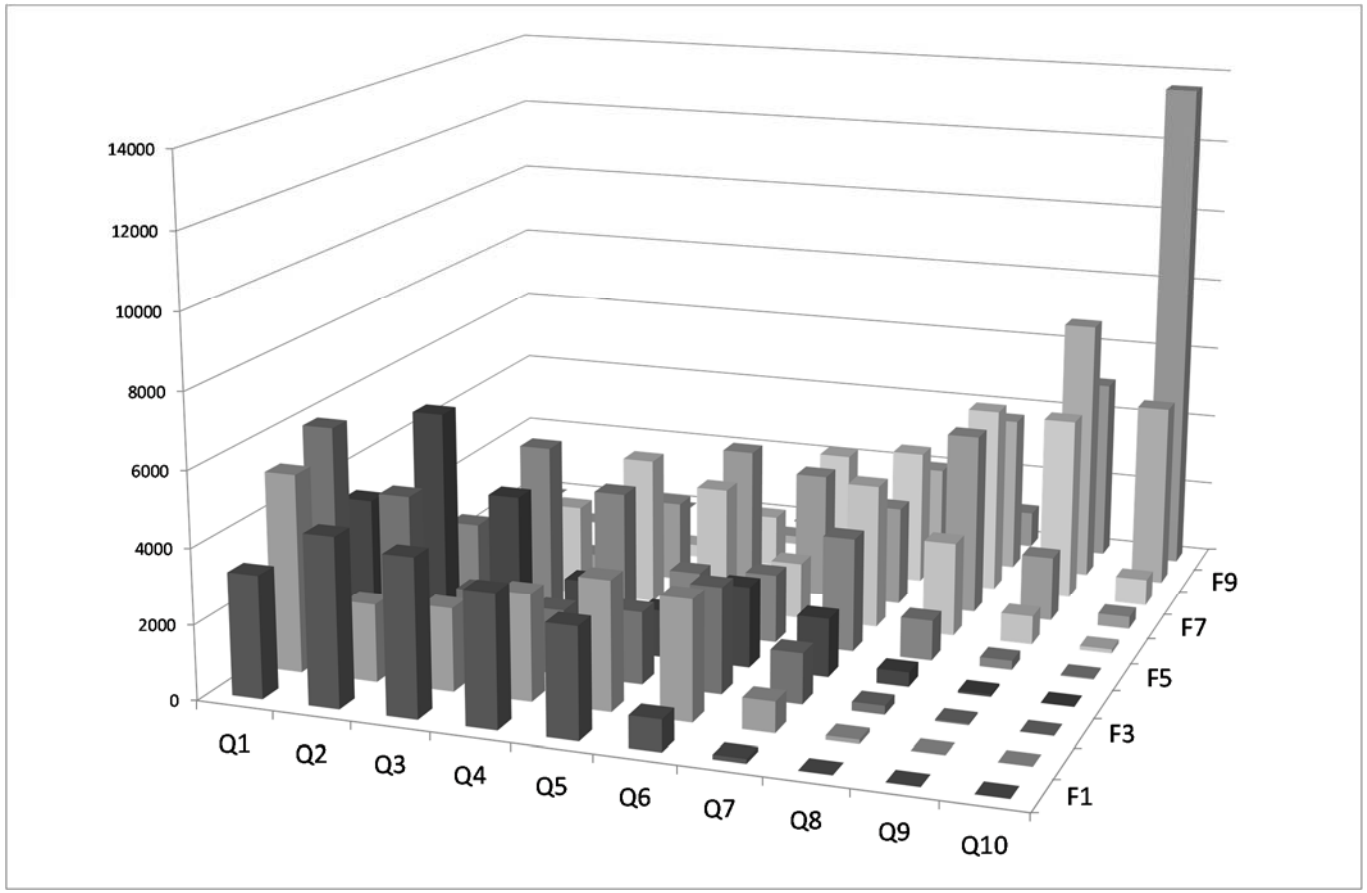
It should be noted that in addition to there being different risk cut-offs for the risk categories when using either QFracture or FRAX scores to define absolute risk, the ranking of patients by risk within the cohort will differ between the two algorithms. It is therefore possible that patients falling into a particular risk category when using the QFracture algorithm may fall into a different risk category when using the FRAX algorithm. Figure 94 shows the

distribution of 200,000 patients eligible for risk assessment under CG146 across the QFracture and FRAX risk categories. It can be seen from Figure 94 that whilst there is some agreement over the categorisation of patients across the two risk scoring algorithms there is not perfect agreement. The correlation between the absolute risk scores was found to be 0.83 and the correlation between the risk categories based on deciles of risk score was found to be 0.76.

Table 34: Summary patient characteristics for each risk category defined by either FRAX or QFracture deciles

Risk category	Mean 10 year risk	Gender, % female	Age, Mean (sd)	BMI Mean (sd)	Prior fracture, %	Steroid use, %	Nursing home resident, %
FRAX							
1st	3.1%	28%	53 (5)	31 (6)	6.4%	0.6%	0.5%
2nd	4.3%	34%	52 (11)	31 (5)	39.4%	1.3%	0.4%
3rd	5.0%	25%	50 (13)	29 (4)	62.3%	0.5%	0.4%
4th	5.6%	23%	49 (14)	26 (4)	73.3%	0.5%	0.5%
5th	6.2%	38%	54 (15)	26 (5)	66.2%	0.9%	0.8%
6th	7.3%	43%	61 (13)	27 (5)	59.5%	1.5%	0.9%
7th	8.8%	48%	66 (10)	28 (4)	57.6%	1.6%	1.0%
8th	10.7%	56%	70 (8)	27 (4)	57.8%	1.8%	1.3%
9th	14.9%	87%	73 (8)	27 (4)	48.6%	3.3%	2.6%
10th	25.1%	99%	81 (7)	26 (4)	68.9%	4.0%	7.6%
QFracture							
1st	0.5%	17%	41 (8)	30 (5)	86.5%	0.6%	0.0%
2nd	0.7%	13%	46 (9	28 (5)	76.8%	0.7%	0.1%
3rd	1.0%	17%	50 (9)	28 (5)	70.2%	1.0%	0.3%
4th	1.4%	27%	55 (9)	28 (5)	60.7%	1.3%	0.4%
5th	2.0%	42%	59 (9)	28 (5)	50.3%	1.6%	0.5%
6th	2.7%	53%	63 (9)	28 (5)	41.6%	1.7%	0.7%
7th	3.9%	65%	66 (9)	28 (5)	37.4%	1.8%	0.7%
8th	5.5%	75%	70 (8)	28 (5)	35.1%	2.1%	1.1%
9th	8.4%	82%	75 (7)	27 (4)	37.4%	2.3%	2.6%
10th	16.0%	90%	83 (6)	26 (4)	45.7%	2.8%	9.6%
ALL	NA	48%	61 (15)	28 (5)	54.2%	1.6%	1.6%

Figure 94 Distribution of patients across FRAX and QFracture risk categories*



*QFracture risk categories are indexed Q1 to Q10 and FRAX risk categories are indexed F1 to F10 with 1 being the lowest risk category in each case

6.2.2.2 Clinical outcomes predicted by the model

Clinical outcomes for 200,000 patients are presented in Table 35 for the basecase scenario in which we have applied the mean persistence with treatment from observational data. Under these assumptions the numbers needed to treat to prevent 1 fracture during the first 6 months (6 months being the duration of persistence with oral bisphosphonates), is lowest for risedronate and highest for oral ibandronate. Given that it is necessary to treat around 2000 patients to prevent 1 fracture during the period of persistence with oral bisphosphonates treatment when using the QFracture risk score, we estimated that we would need to simulate approximately 2 million patients to obtain stable estimates of the benefits of treatment in each risk category. This is because we would expect around 1000 fractures to be prevented across a cohort of 2 million patients with around 1% falling within the lowest risk category of QFracture. Therefore the costs and QALY implications of treatment would be based on around 10 fractures in the lowest risk category of QFracture when using a cohort of 2 million patients.

It can be seen from Table 35 that the number of fractures occurring in the first 6 months when using the FRAX algorithm are higher than when using the QFracture algorithm. This is because the absolute risk predicted by FRAX is higher than the absolute risk predicted by QFracture in 98% of patients.

Table 35: Clinical outcomes for 200,000 patients when applying mean persistence from observational studies

	Fractures occurring in the first 6 months after starting treatment (the mean duration of persistence with treatment for oral bisphosphonates)					NNT to prevent 1 fracture occurring in the first 6 months after starting treatment
Treatment strategy	**Hip fractures (including other femoral)**	**Vertebral fractures**	**Proximal humerus fractures (including tibia and fibula)**	**Wrist (including all other additional sites)**	**All fracture sites combined**	
FRAX						
No treatment	216	146	143	495	1000	
Alendronate	170	72	109	400	751	803
Risedronate	175	80	98	360	713	697
Ibandronate (oral)	182	72	109	400	763	844
Ibandronate (i.v.)	182	75	130	400	787	939
Zoledronate	202	66	99	389	756	820
QFracture						
No treatment	121	63	67	177	428	1770
Alendronate	99	19	52	145	315	1550
Risedronate	102	24	45	128	299	1942
Ibandronate (oral)	109	19	52	145	325	2222
Ibandronate (i.v.)	109	19	65	145	338	1835
Zoledronate	115	15	48	141	319	1770

NNT = number needed to treat

6.2.2.3 Presentation of cost-effectiveness results

The mean costs and QALYs from the PSA are presented as the basecase results. These were considered to be preferable to estimates obtained using midpoint (mean or median) parameter inputs because we believe that there may be a non-linear relationship between parameter values and model outcomes. The data presented were obtained from a total patient population of 2 million across all 10 risk categories with 1 parameter sample per patient. Therefore, approximately 200,000 patients and 200,000 parameter samples informed the estimates for each risk category.

Full results tables for the basecase scenario including an incremental analysis for each risk category for QFracture and FRAX are presented in Appendices 10 and 11, respectively. Results have been summarised below by plotting the incremental net benefit (INB) compared to a strategy of no treatment when assuming that a QALY is valued at £20,000. INB has been plotted instead of incremental cost-effectiveness ratios (ICERs) as these can be difficult to interpret when the QALY gain is negative, which was the case for some treatments in some risk categories. The cost-effectiveness plane has not been presented as a minimum of 20 graphs would be needed to present results across all 10 risk categories for both QFracture and FRAX. We used non-parametric regression to estimate the cost-effectiveness acceptability curves (CEACs). This allows variation in the costs and QALYs due to parameter uncertainty to be separated from variation due to patient-level stochastic variability.

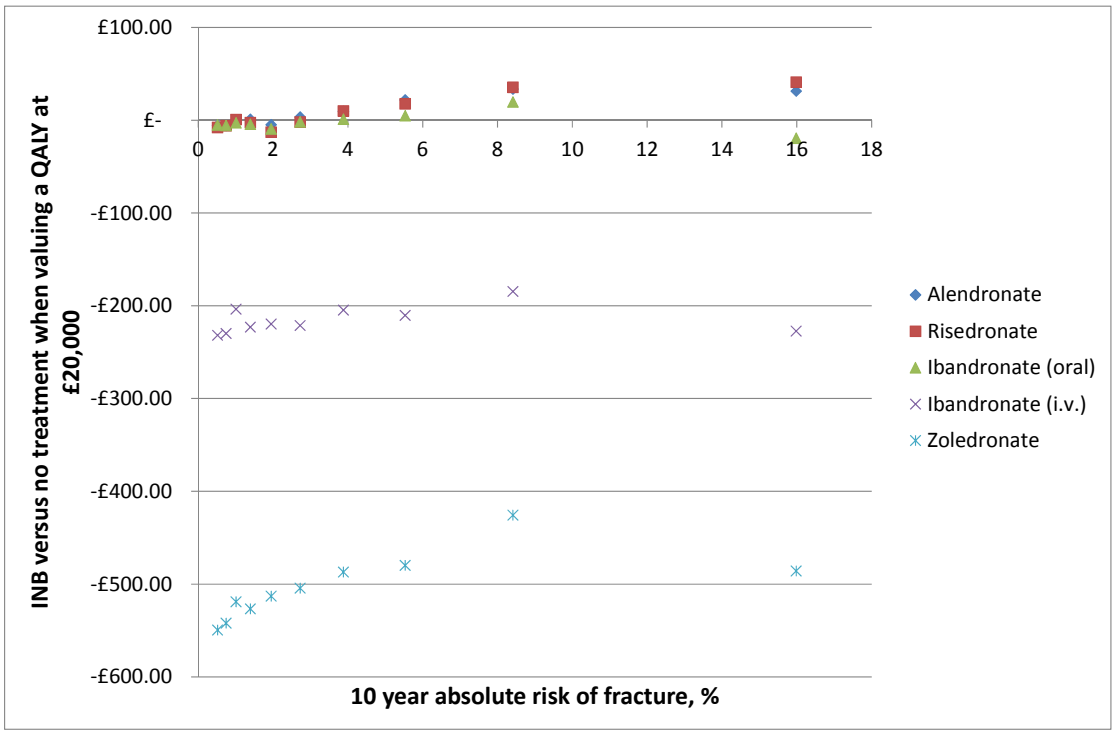
Structural sensitivity analyses have been conducted by fixing parameter values at their midpoint value. Whilst it would have been preferable to re-run the PSA for each structural sensitivity analysis this was not possible within the time constraints. The PSA was re-run for the sensitivity analysis which involved changing the HRs for treatment as we considered it important in this case to capture the underlying joint distribution for the HRs. For the sensitivity analyses on adverse event rates and the sensitivity analysis examining alternative treatment costs for zoledronate, the outputs of the basecase PSA model were adjusted as these adjustments could be made without re-running the PSA. For all other sensitivity analyses, the model using midpoint parameter estimates was run for 2.2 million patients.

6.2.2.4 Summary cost-effectiveness results for the basecase scenario when using QFracture

Figure 95 summarises the cost-effectiveness results across the 10 risk categories when using QFracture to estimate absolute risk. It shows the INB, in monetary terms, when valuing a QALY at £20,000, when compared with a strategy of no treatment. Each point shows the mean INB and the mean 10 year absolute risk of fracture for one risk category for a particular bisphosphonate treatment. It can be seen that the mean INB is close to zero for all three oral bisphosphonates across the first 6 risk categories, which have mean absolute risks ranging from 0.5% to 2.7%, and the estimates are all very close together.

Detailed results tables providing a full incremental analysis are provided in Appendix 10. It can be seen from these that in the 3rd, 4th and 6th risk categories (mean absolute risks of 1.0%, 1.4% and 2.7%) at least one of the oral bisphosphonates has a positive INB but the absolute INB is still small and close to zero. In the 5th risk category (mean absolute risk of 2%) it is below zero for all three oral bisphosphonates. The INB is positive for all 3 oral bisphosphonates from the 7th to the 10th risk categories (mean absolute risk of 3.9% and above). A strategy of no treatment has the maximum net benefit in the 1st, 2nd and 5th risk categories (mean absolute risks of 0.5%, 0.7% and 2.0%) and when a QALY is valued at either £20,000 or £30,000 (See Tables in Appendix 10 for INB at £30,000). In the other risk categories the treatment with maximum net benefit is always either alendronate or risedronate. Oral ibandronate does not fall on the cost-effectiveness frontier in any risk category when using QFracture to estimate absolute risk. The difference between oral ibandronate and the other two oral bisphosphonates becomes more apparent in the higher risk categories. This is due to marginally less favourable efficacy data for oral ibandronate which becomes more important as the risk increases. For the i.v. bisphosphonates the INB is negative across all 10 risk categories when valuing a QALY at either £20,000 or £30,000 (See Tables in Appendix10 for INB at £30,000).

Figure 95 Incremental net benefit (when valuing QALY at £20,000) compared with no treatment against 10 year fracture risk from QFracture



The full data from the PSA for whole population (2 million patients with 1 parameter sample per patient) were used in a non-parametric regression which estimated the relationship between INB and absolute fracture risk estimated by QFracture. The regression prediction is shown in Figure 96 with a close up provided in Figure 97 of the lower risk range. The results here differ from those presented in Figure 95 because the non-parametric regression method is able to average over the stochastic uncertainty associated with the individual level patients whilst simultaneously estimating the relationship between INB and absolute risk. It can be seen that alendronate and risedronate have increasing INB as risk increases. A strategy of no treatment is predicted to have the greatest net benefit for the lowest risk patients. Table 36 summarises the thresholds over which each treatment has a positive INB compared with no treatment (when valuing a QALY at £20,000) and the range over which each treatment has the maximum INB based on the non-parametric regression. Alendronate is predicted to have the maximum net benefit from 1.5% and risedronate is predicted to have the maximum net benefit from 7.2% upwards. Oral and i.v. ibandronate have differing relationships with absolute risk which may reflect the fact that different efficacy data were applied. However, the results for i.v. ibandronate should be treated with caution as no fracture data were available for this treatment and data from other ibandronate dosing regimens were applied. It should also be noted that the regression may predict INB less well in higher risk patients as

only 10% of the population had a risk score above 11%. It is also important to consider the uncertainty around the INB estimates by considering the CEACs.

Table 36 QFracture absolute risk thresholds obtained from regression of incremental net benefit (INB) compared with no treatment over absolute risk (when valuing a QALY at £20,000)

Treatment	**Range over which INB is positive compared to no treatment**	**Range over which INB greater than for all over treatments**
No treatment	NA	<1.5%
Alendronate	>1.5%	>1.5 and <7.2%
Risedronate	>2.3%	>7.2%
Ibandronate (oral)	>4.2 and <13.1%	Never
Ibandronate (i.v.)	>75.5%	Never
Zoledronate	Never	Never

Figure 96 Regression for incremental net benefit (when valuing QALY at £20,000) compared with no treatment against 10 year fracture risk from QFracture

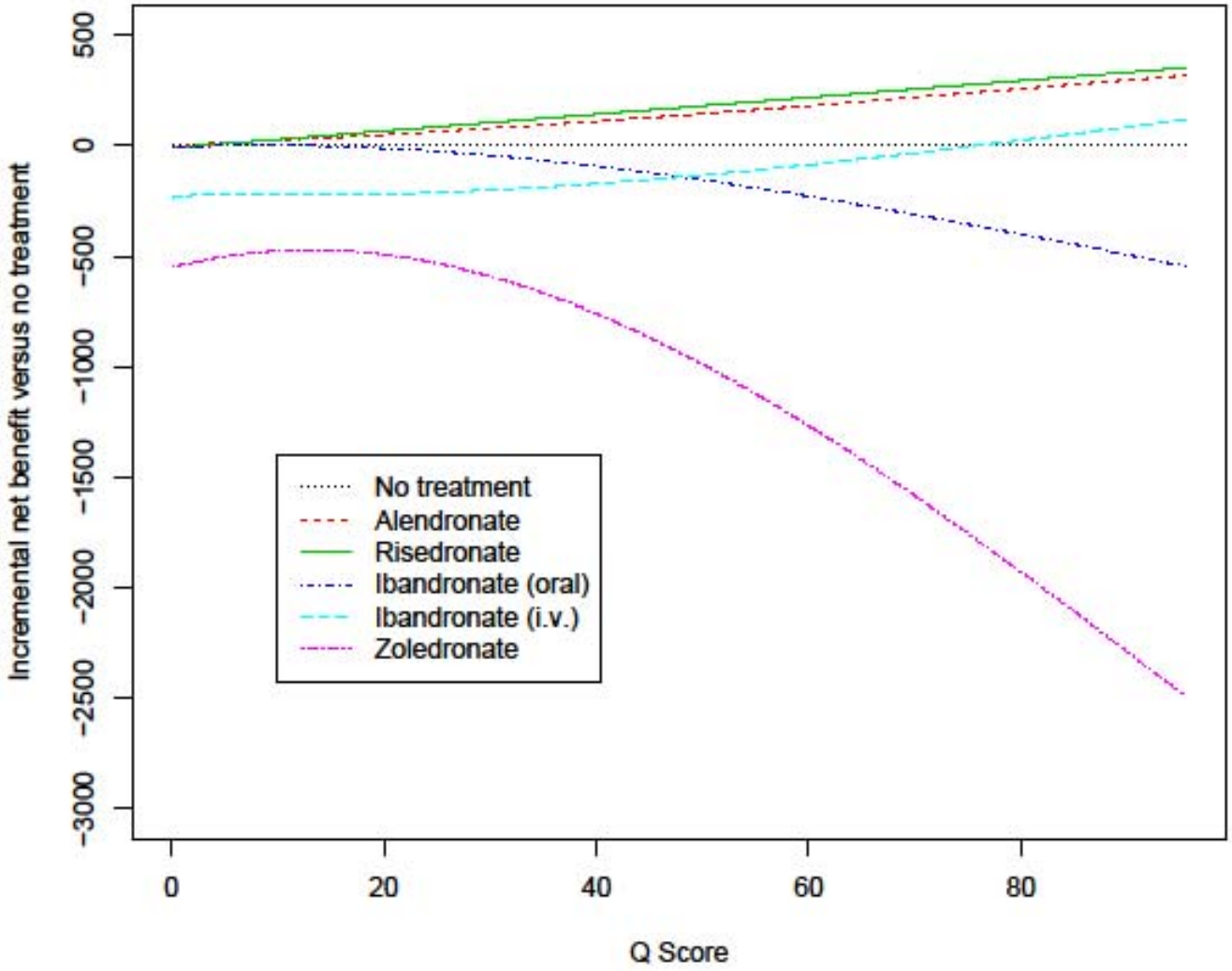


Figure 97 Close up of regression for incremental net benefit (when valuing QALY at £20,000) compared with no treatment against 10 year fracture risk from QFracture

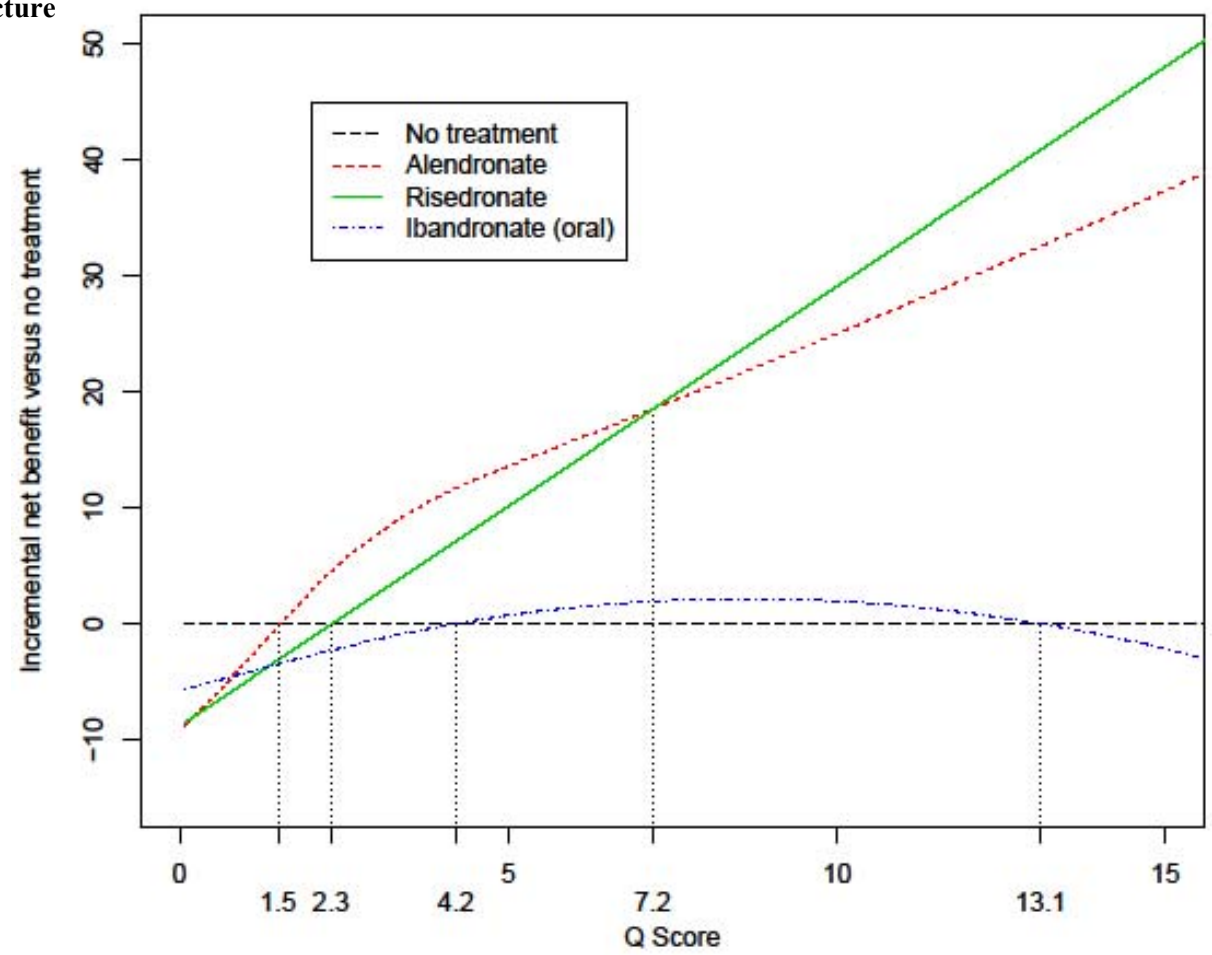


Figure 98 to Figure 107 present the CEACs for each of the risk categories when using QFracture to determine absolute risk. It can be seen that in the first and second risk categories (mean absolute risk of 0.5% and 0.7%), the no treatment strategy has a much higher probability of being optimal, when valuing a QALY at £20,000 than any of the other strategies. However, in the 3rd risk category (mean absolute risk of 1.0%) no treatment has the third highest probability of being most cost-effective with both risedronate and oral ibandronate having a greater probability when valuing a QALY at either £20,000 or £30,000. Although all three oral bisphosphonates have a positive INB compared with no treatment in the 7th risk category (mean absolute risk of 3.9%) when valuing a QALY at £20,000, no treatment has a higher probability of being cost-effective than either risedronate or oral ibandronate suggesting that there is still considerable uncertainty regarding the relative cost-effectiveness of oral bisphosphonates.

The i.v. bisphosphonates have a low probability of being optimal when valuing a QALY at £20,000 even in the highest risk categories although by the 10th risk category (mean absolute risk of 16.0%) they have a similar probability of being cost-effective as no treatment.

Figure 98 Cost-effectiveness acceptability curve for QFracture risk category 1 (mean absolute risk of 0.5%)

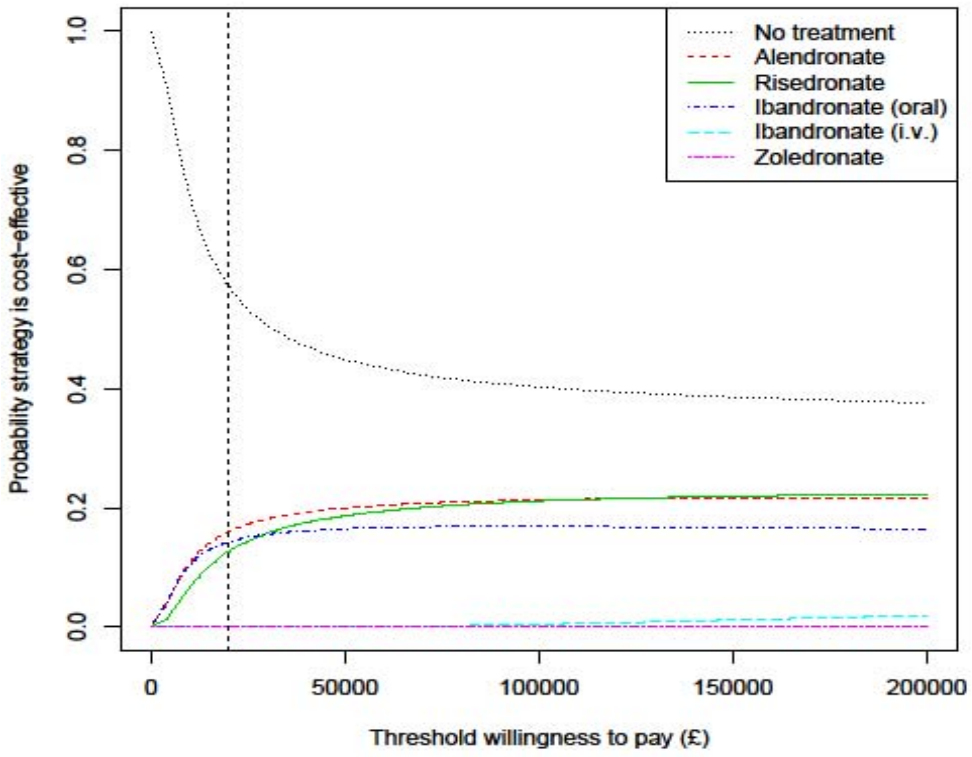


Figure 99 Cost-effectiveness acceptability curve for QFracture risk category 2 (mean absolute risk of 0.7%)

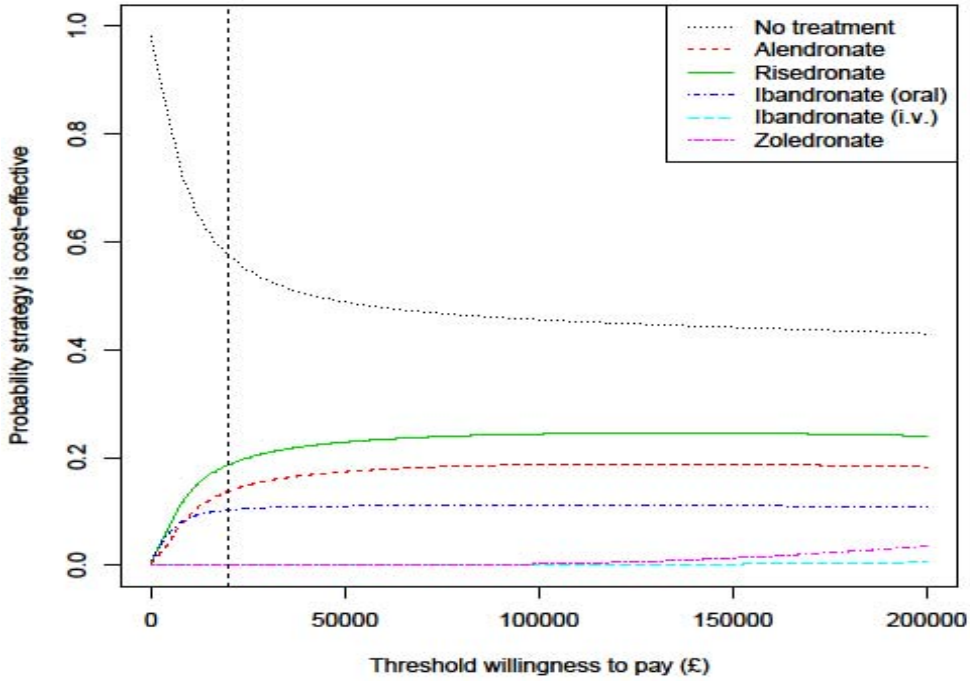


Figure 100 Cost-effectiveness acceptability curve for QFracture risk category 3 (mean absolute risk of 1.0%)

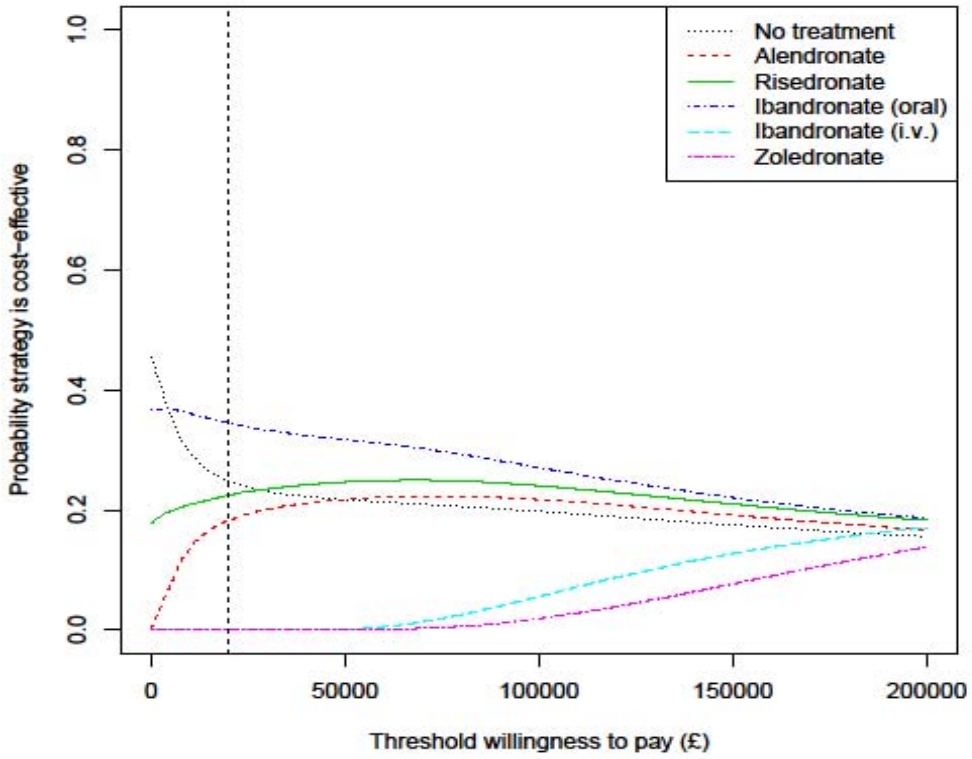


Figure 101 Cost-effectiveness acceptability curve for QFracture risk category 4 (mean absolute risk of 1.4%)

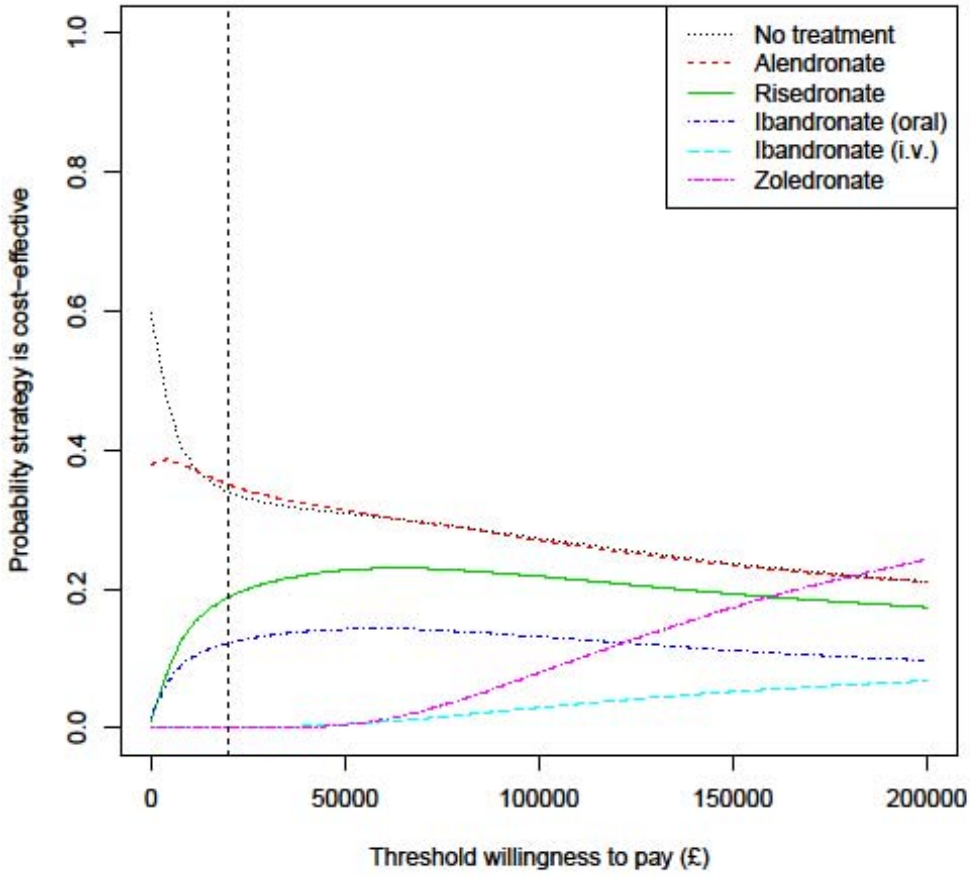


Figure 102 Cost-effectiveness acceptability curve for QFracture risk category 5 (mean absolute risk of 2.0%)

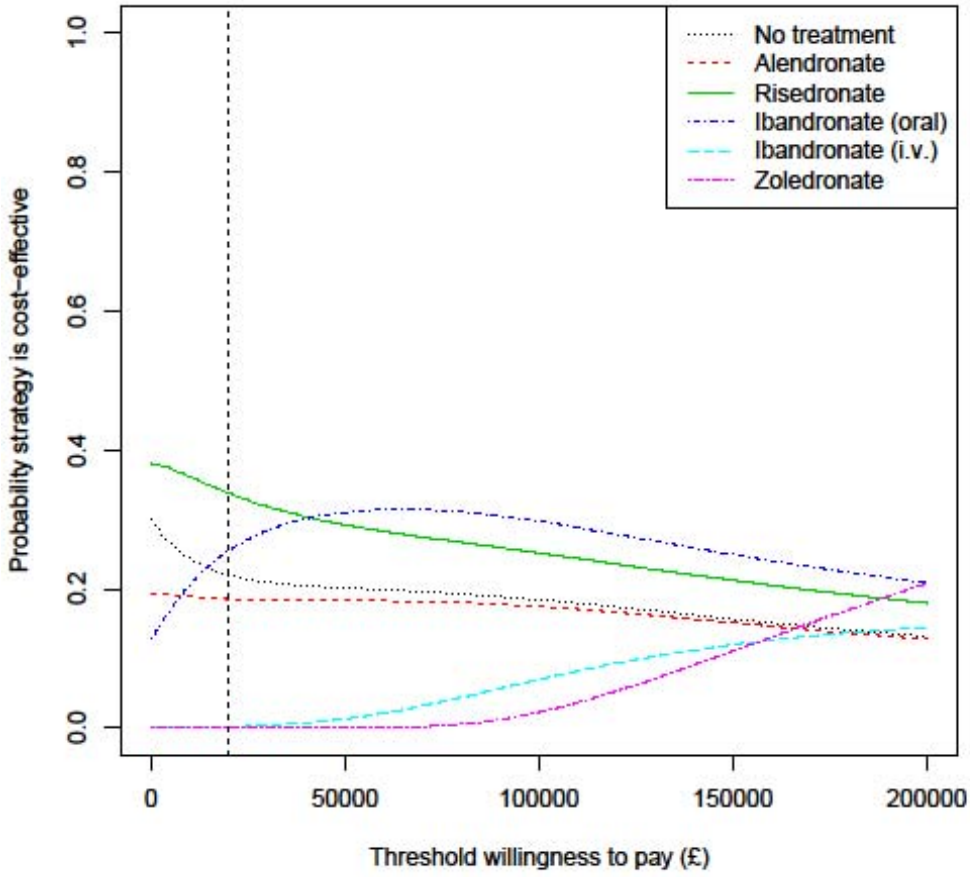


Figure 103 Cost-effectiveness acceptability curve for QFracture risk category 6 (mean absolute risk of 2.7%)

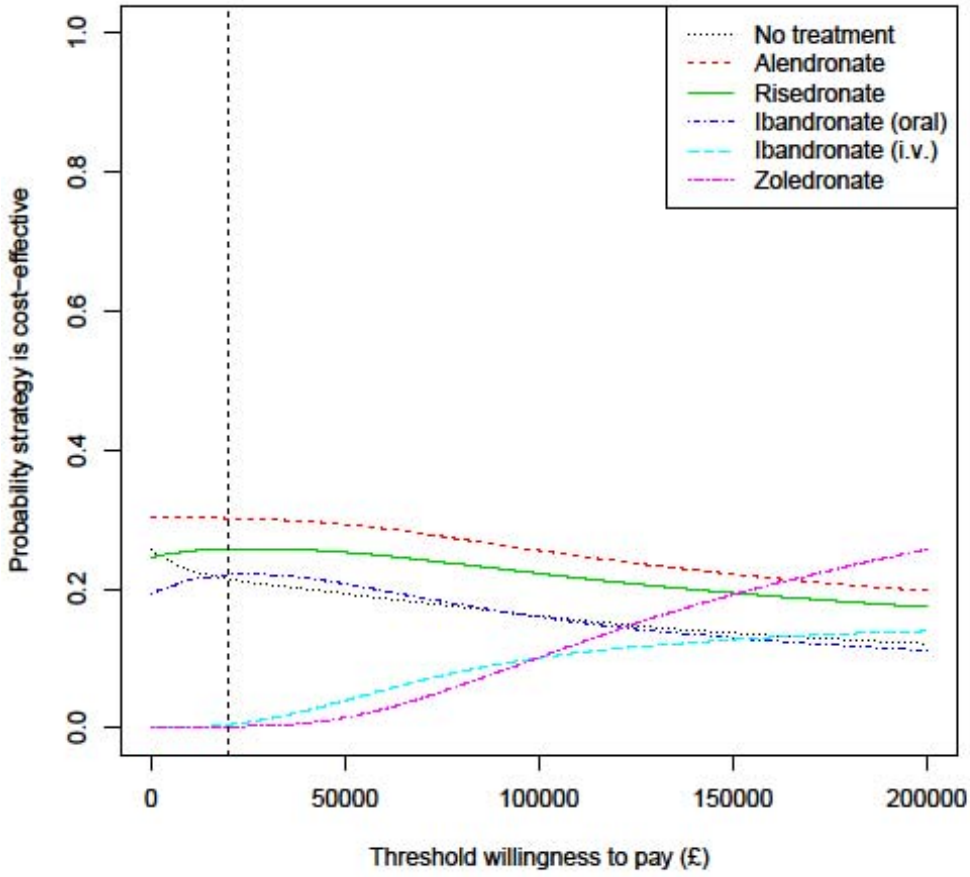


Figure 104 Cost-effectiveness acceptability curve for QFracture risk category 7 (mean absolute risk of 3.9%)

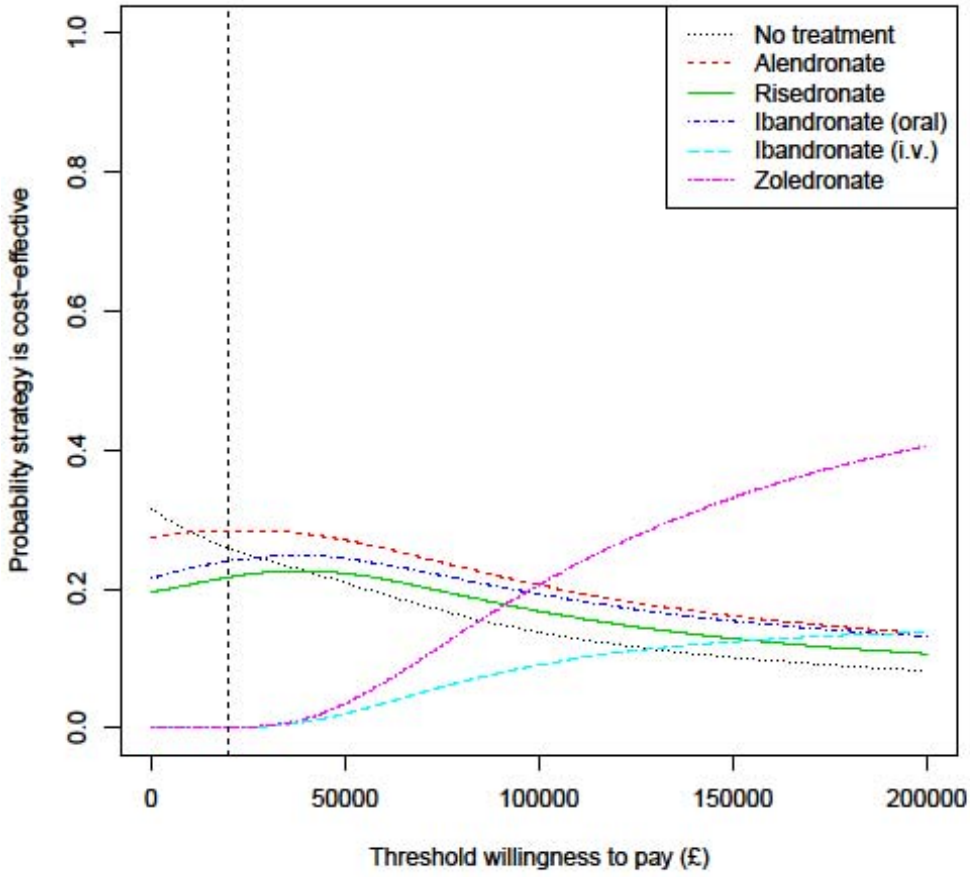


Figure 105 Cost-effectiveness acceptability curve for QFracture risk category 8 (mean absolute risk of 5.5%)

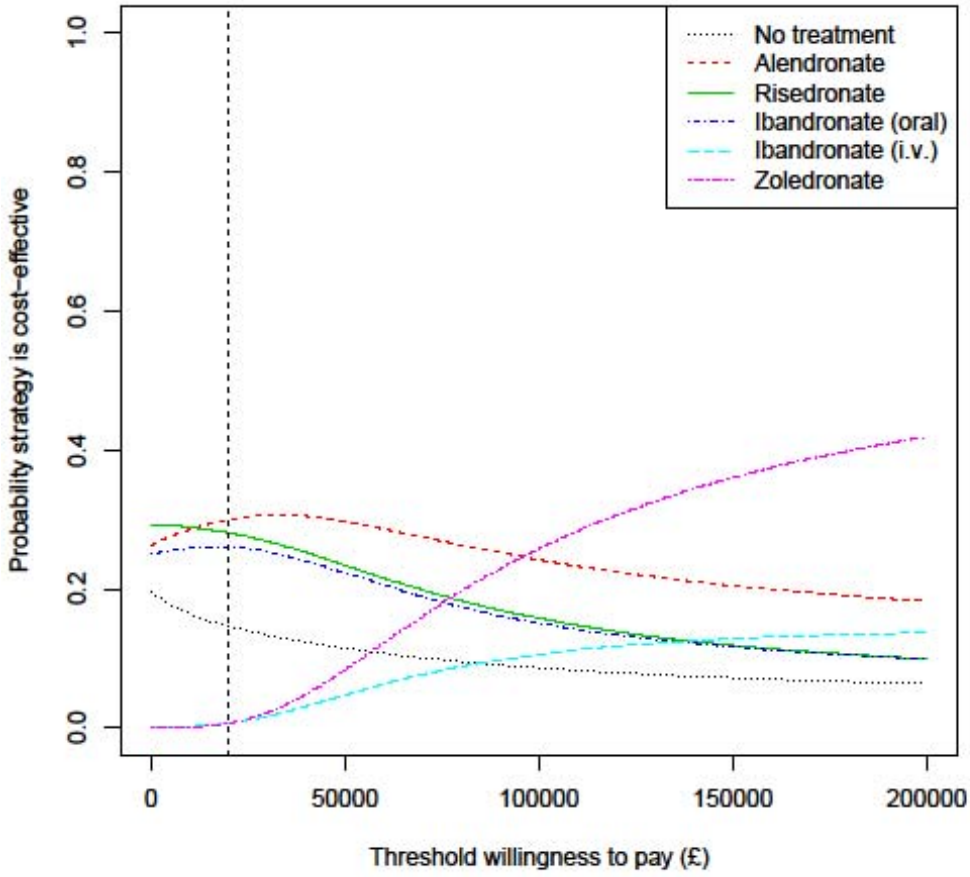


Figure 106 Cost-effectiveness acceptability curve for QFracture risk category 9 (mean absolute risk of 8.4%)

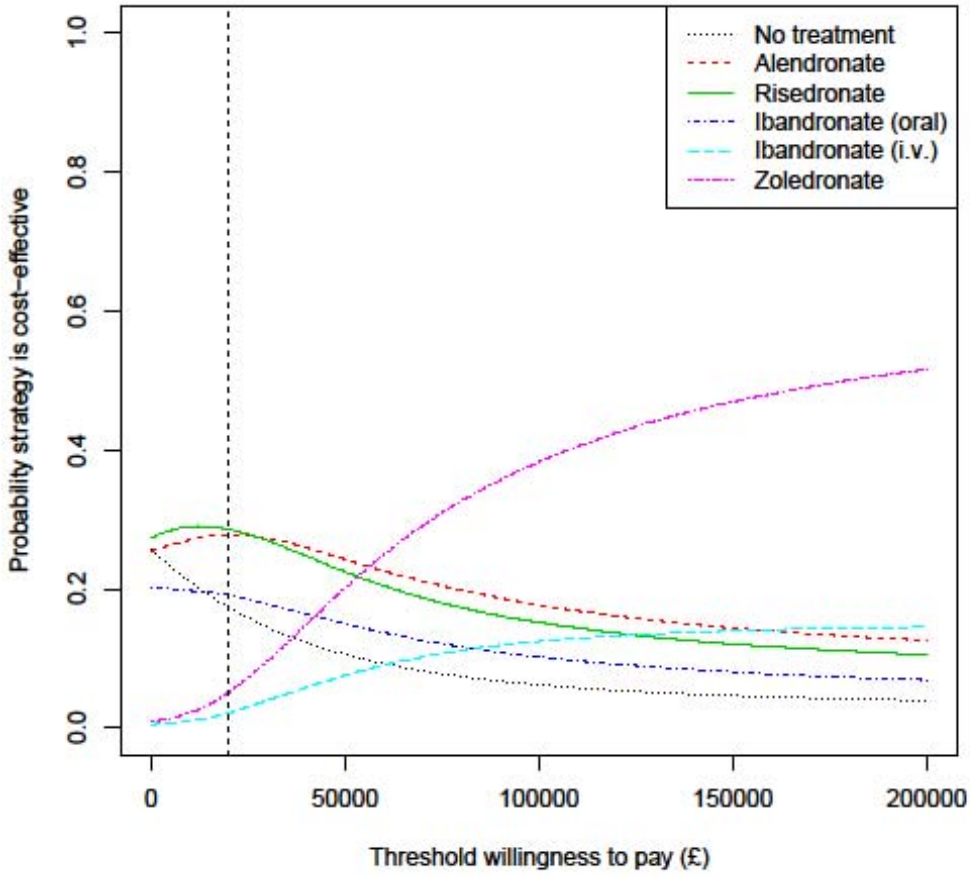
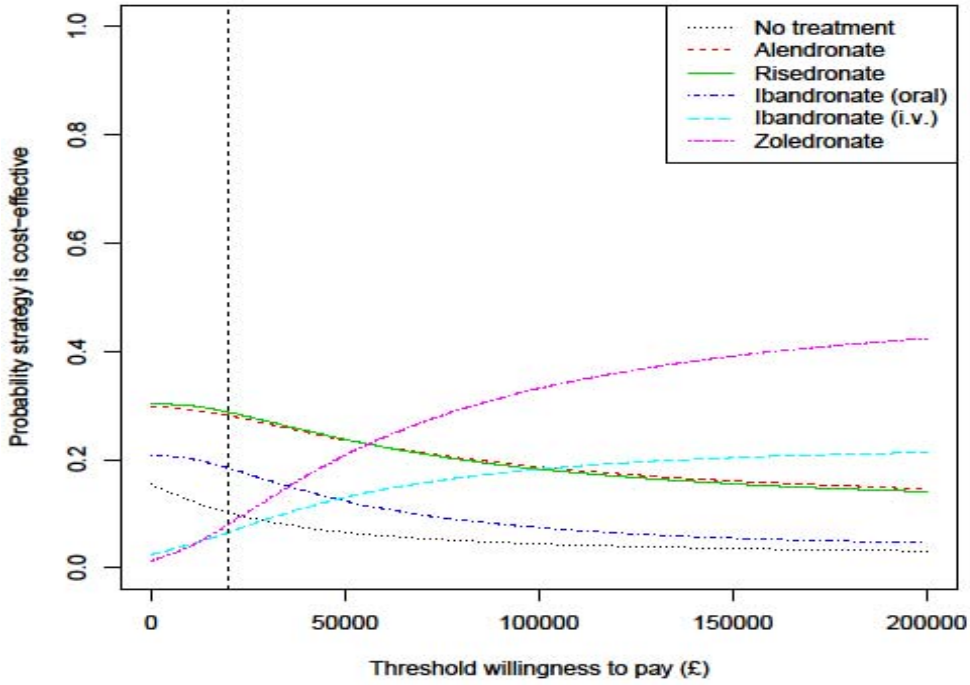


Figure 107 Cost-effectiveness acceptability curve for QFracture risk category 10 (mean absolute risk of 16.0%)

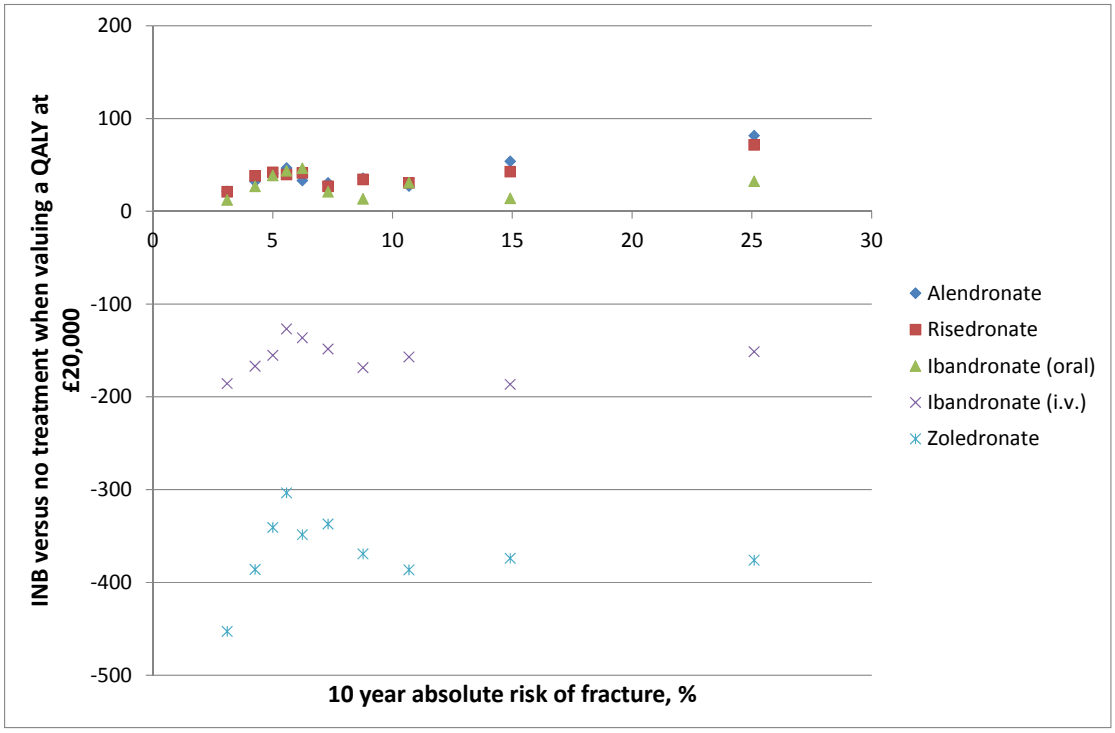


6.2.2.3 Summary cost-effectiveness results for the basecase scenario when using FRAX

Figure 108 summarises the cost-effectiveness results across the 10 risk categories for FRAX. It shows the incremental net benefit (INB) for each bisphosphonate treatment when compared with no treatment plotted against the 10 year absolute risk of fracture. Each point shows the mean INB and the mean 10 year absolute risk of fracture for one risk category when valuing a QALY at £20,000. It can be seen that the INB compared to no treatment does not have a simple relationship with absolute risk when using FRAX to define absolute risk. At first the INB rises but then later it falls and rises again. This may reflect the differing patient characteristics across the risk categories. However, it can be seen that the mean INB compared to no treatment is above zero for all oral bisphosphonates across all 10 risk categories. The detailed results tables provided in Appendix 10 show that none of the bisphosphonates is consistently more cost-effective than the others with all three having the highest INB (when valuing a QALY at £20,000) in at least one risk category and all three being dominated by another oral bisphosphonate in at least 1 risk category.

Contrastingly, the mean INB for the two i.v. bisphosphonates are below zero across all 10 risk categories. This remains the case even when valuing a QALY at £30,000 (See Tables in Appendix 11). Furthermore, i.v. ibandronate is always extendedly dominated by the other treatment strategies across all 10 risk categories for FRAX.

Figure 108 Incremental net benefit (when valuing QALY at £20,000) compared with no treatment against 10 year fracture risk from FRAX



The full data from the PSA for the whole population (2 million patients with 1 parameter sample per patient) were used in a non-parametric regression which estimated the relationship between INB and absolute fracture risk estimated by FRAX. The regression prediction is shown in Figure 109 with a close up shown in Figure 110 for the lower risk range. The results here differ from those presented in Figure 108 because non-parametric regression is able to average over the stochastic uncertainty associated with the individual level patients whilst simultaneously estimating the relationship between INB and absolute risk. It can be seen that alendronate and risedronate have increasing INB as risk increases. All three oral bisphosphonates have positive INB compared with no treatment across the full range of absolute risk observed in the modelled population. Table 37 summarises the thresholds over which each treatment has a positive INB compared with no treatment (when valuing a QALY at £20,000) and the range over which each treatment has the maximum INB based on the non-parametric regression. Ibandronate is predicted to have the maximum INB up to an absolute

risk level of 8.6%. Alendronate is predicted to have the maximum net benefit from 8.6%% to 38.5% and risedronate is predicted to have the maximum net benefit from 38.5% upwards. The INB compared with no treatment is negative for both the i.v. bisphosphonates across the full range of absolute risk observed in the modelled population when using FRAX to estimate absolute risk. By comparing Figure 96 and Figure 109 it can be seen that the relationship between INB and absolute risk for the i.v. bisphosphonates appears to differ when using FRAX and QFracture for patients with an absolute risk above 20%. This may not reflect a true difference however, as the estimates above 11% for QFracture and above 18% for FRAX are only informed by one tenth of the modelled population and therefore it is also important to consider the uncertainty in these estimates of mean INB by considering the CEACs.

Table 37 FRAX absolute risk thresholds obtained from regression of incremental net benefit compared with no treatment over absolute risk (when valuing a QALY at £20,000)

Treatment	Range over which INB is positive compared to no treatment	Range over which INB greater than for all over treatments
No treatment	NA	Never
Alendronate	Whole range observed in modelled population	>8.6 and <38.5%
Risedronate	Whole range observed in modelled population	>38.5%
Ibandronate (oral)	Whole range observed in modelled population	<8.6%
Ibandronate (i.v.)	Never	Never
Zoledronate	Never	Never

Figure 109 Regression for incremental net benefit (when valuing QALY at £20,000) compared with no treatment against 10 year fracture risk from FRAX

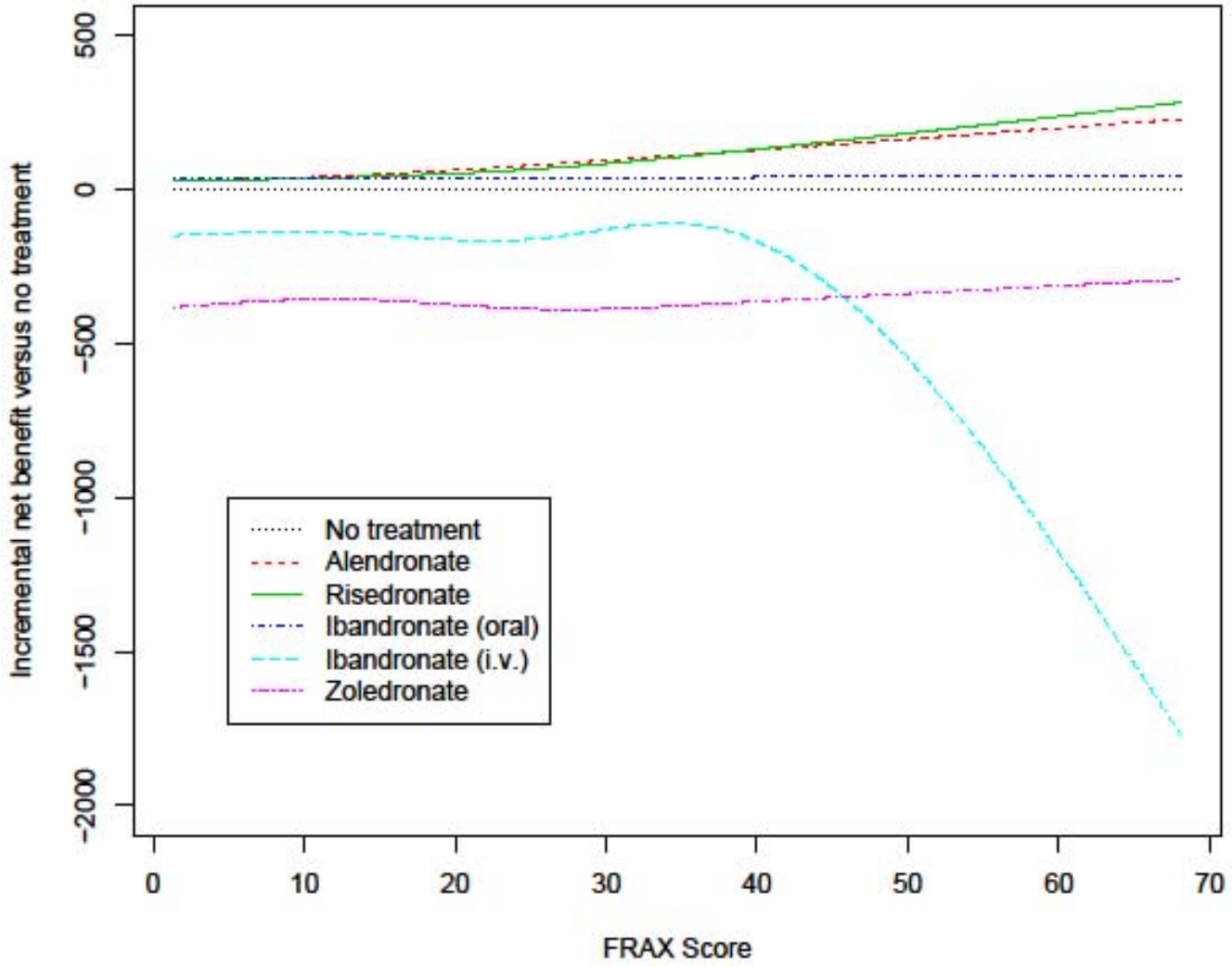


Figure 110 Close up of regression for incremental net benefit (when valuing QALY at £20,000) compared with no treatment against 10 year fracture risk from FRAX

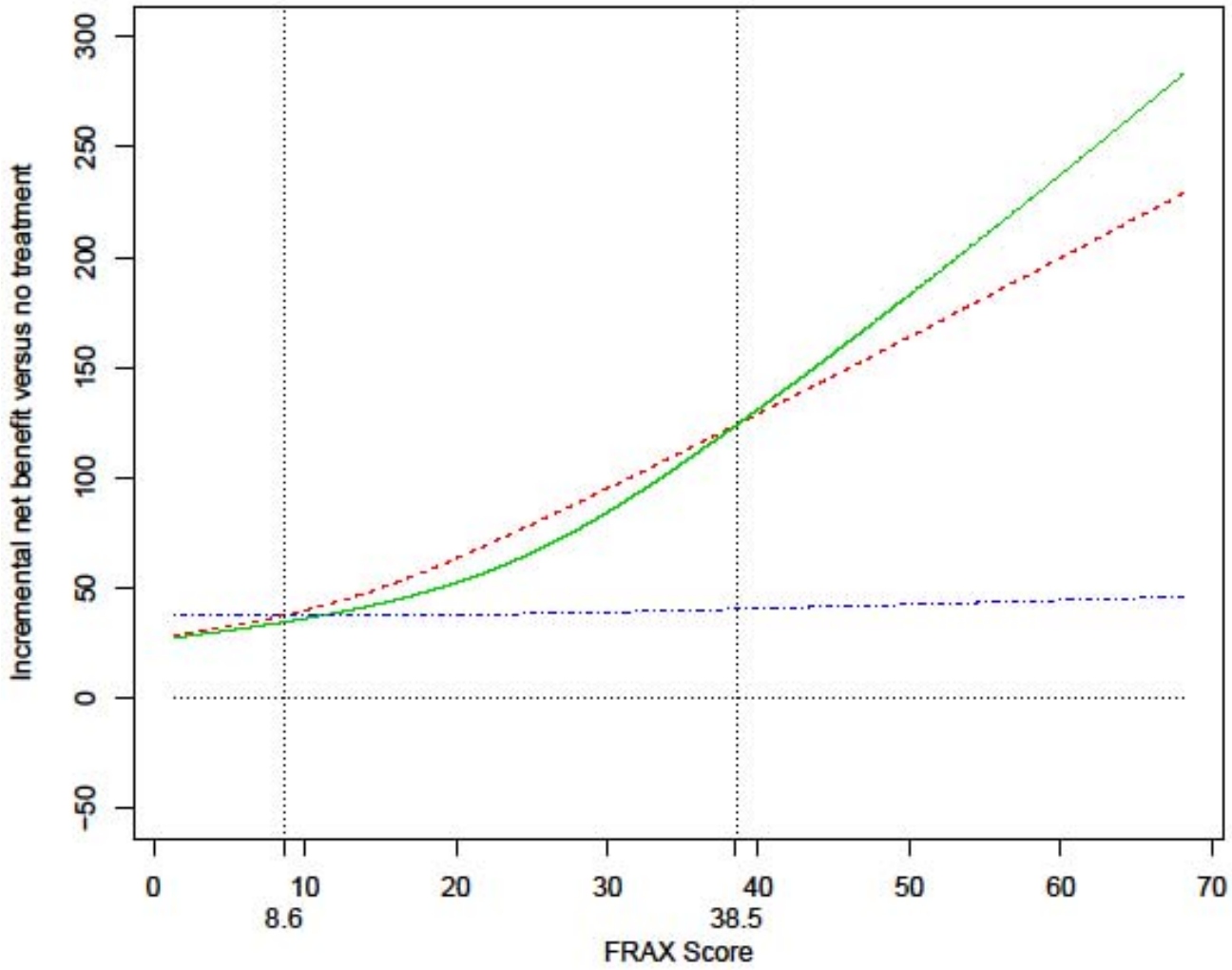


Figure 111 to Figure 120 show the CEACs for the ten FRAX risk categories. It can be seen that the strategy of no treatment has a low probability of being most cost-effective, when valuing a QALY at £20,000, across all ten risk categories. The i.v. bisphosphonates always have a lower probability of being optimal compared to no treatment or the oral bisphosphonates until risk category 8 (mean absolute risk of 10.7%) when i.v. zoledronate has a higher probability that no treatment. In FRAX risk category 10 (mean absolute risk of 25.1%), i.v. zoledronate has the highest probability of being cost-effective, when valuing QALY at £20,000 and i.v. ibandronate has a higher probability than oral ibandronate. However, it should be noted that the mean INB for both the i.v. bisphosphonates is negative in this risk category when valuing a QALY at £20,000.

Figure 111 Cost-effectiveness acceptability curve for FRAX risk category 1 (mean absolute risk of 3.1%)

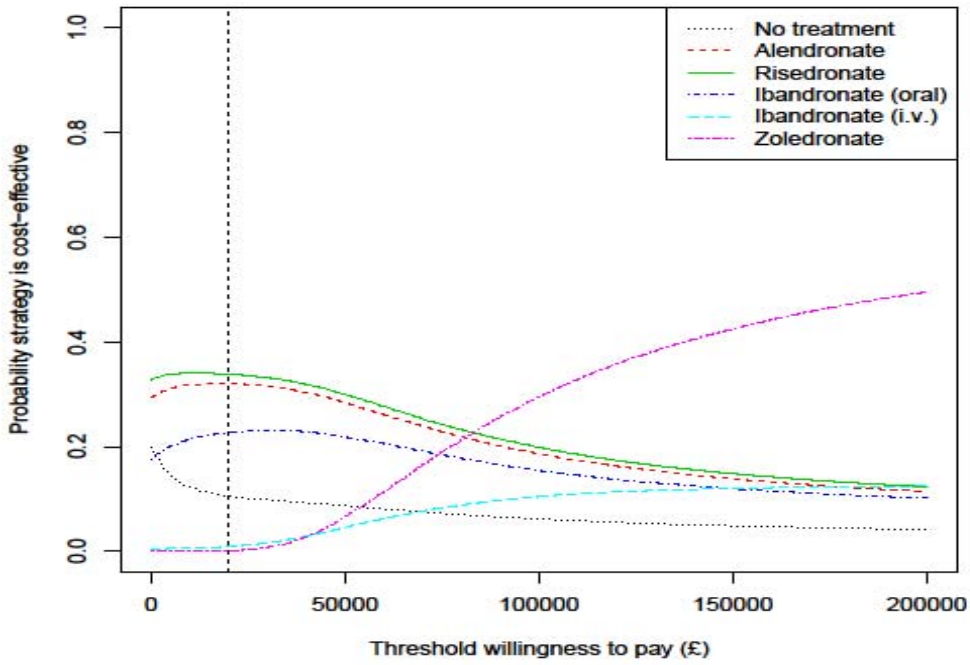


Figure 112 Cost-effectiveness acceptability curve for FRAX risk category 2 (mean absolute risk of 4.3%)

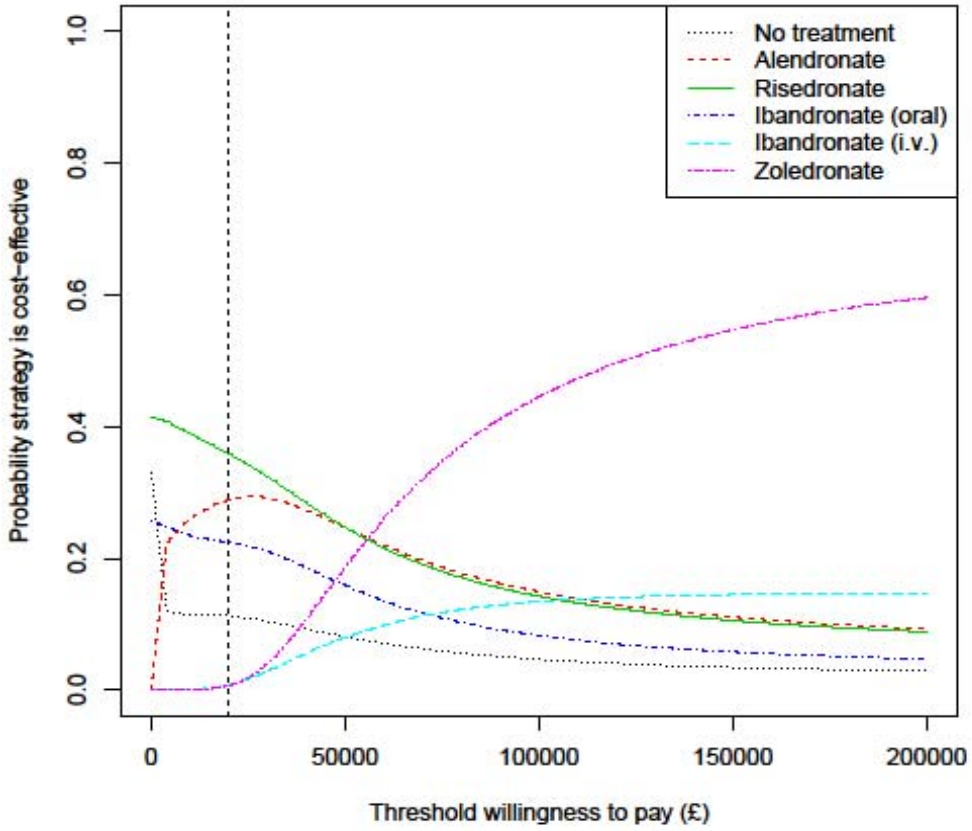


Figure 113 Cost-effectiveness acceptability curve for FRAX risk category 3 (mean absolute risk of 5.0%)

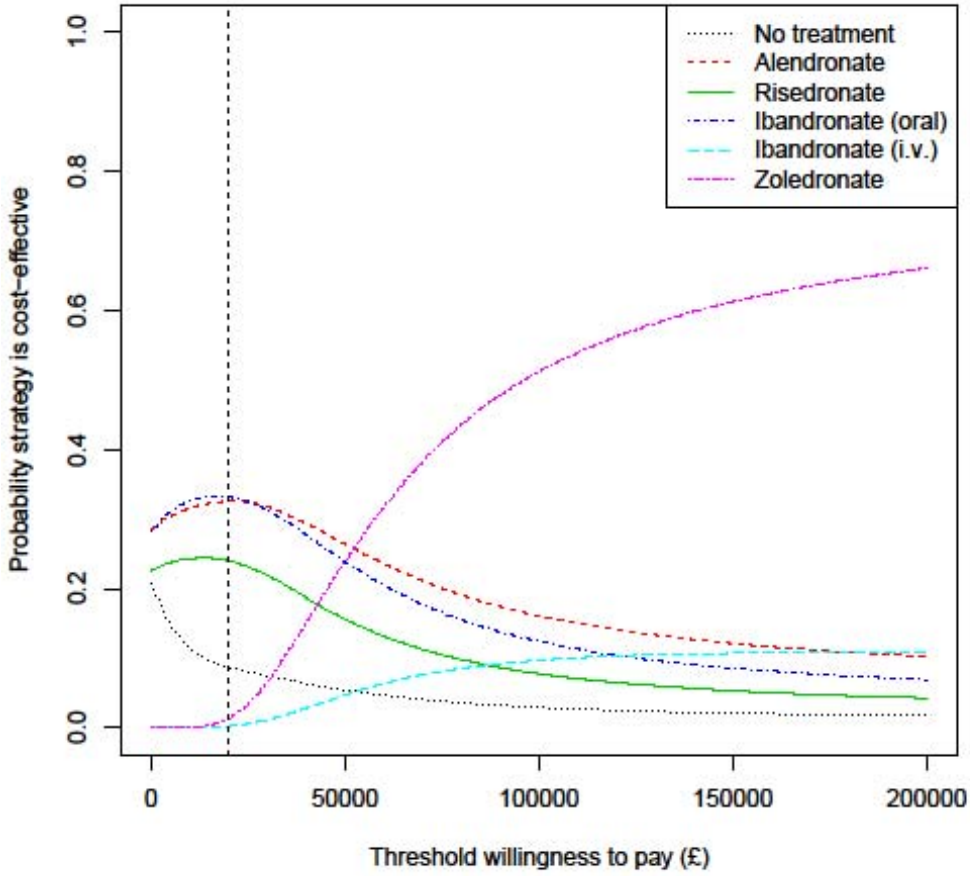


Figure 114 Cost-effectiveness acceptability curve for FRAX risk category 4 (mean absolute risk of 5.6%)

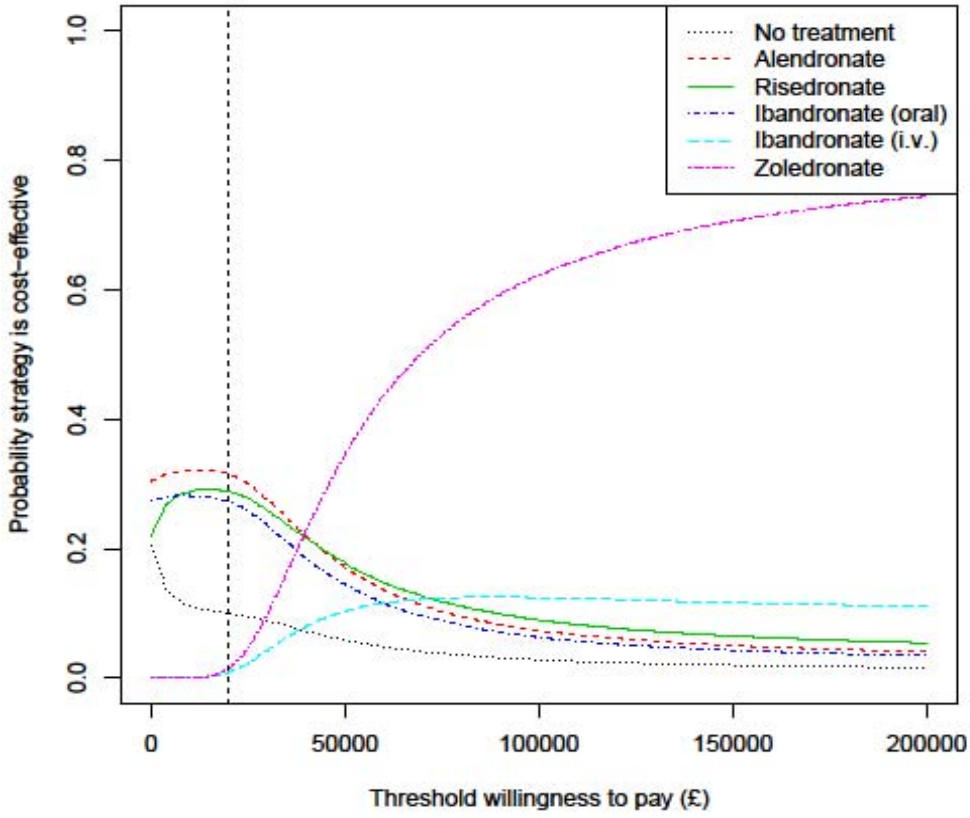


Figure 115 Cost-effectiveness acceptability curve for FRAX risk category 5 (mean absolute risk of 6.2%)

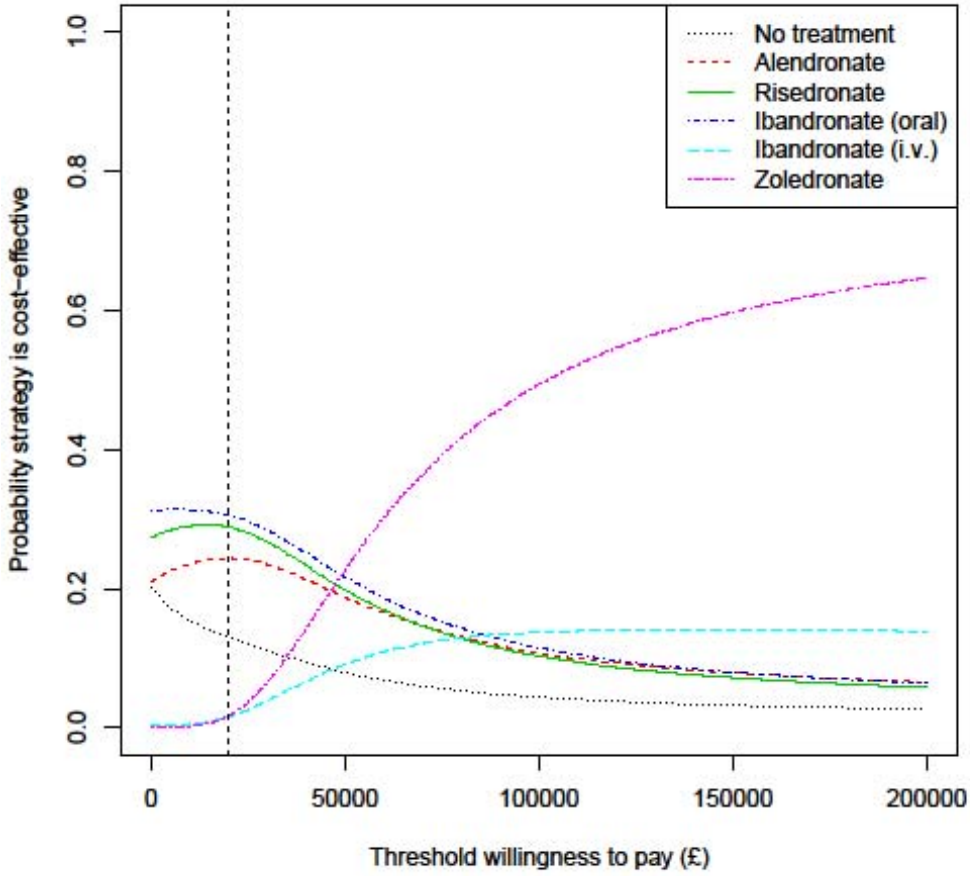


Figure 116 Cost-effectiveness acceptability curve for FRAX risk category 6 (mean absolute risk of 7.3%)

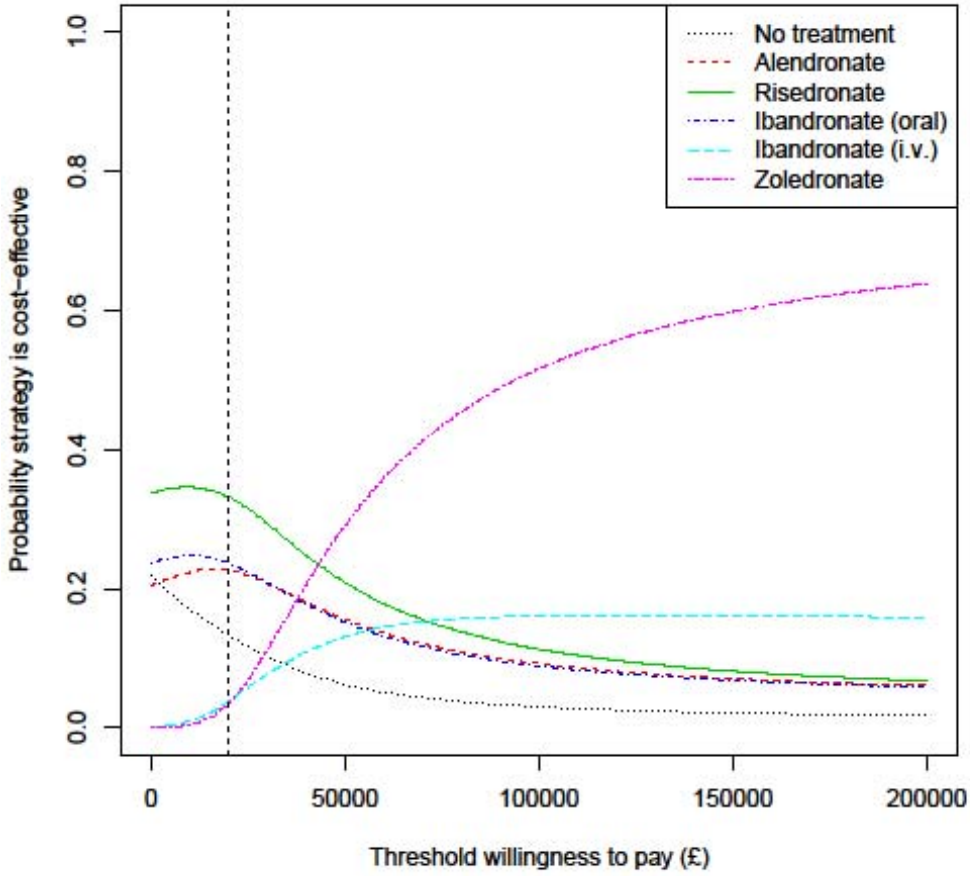


Figure 117 Cost-effectiveness acceptability curve for FRAX risk category 7 (mean absolute risk of 8.8%)

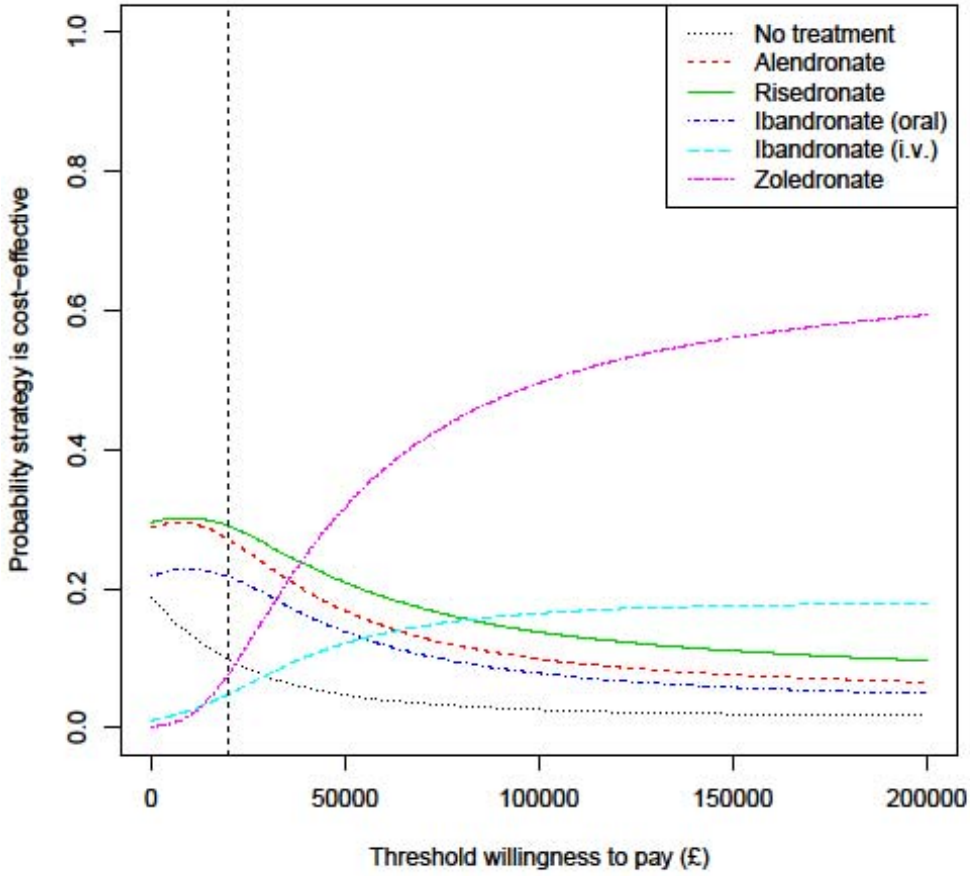


Figure 118 Cost-effectiveness acceptability curve for FRAX risk category 8 (mean absolute risk of 10.7%)

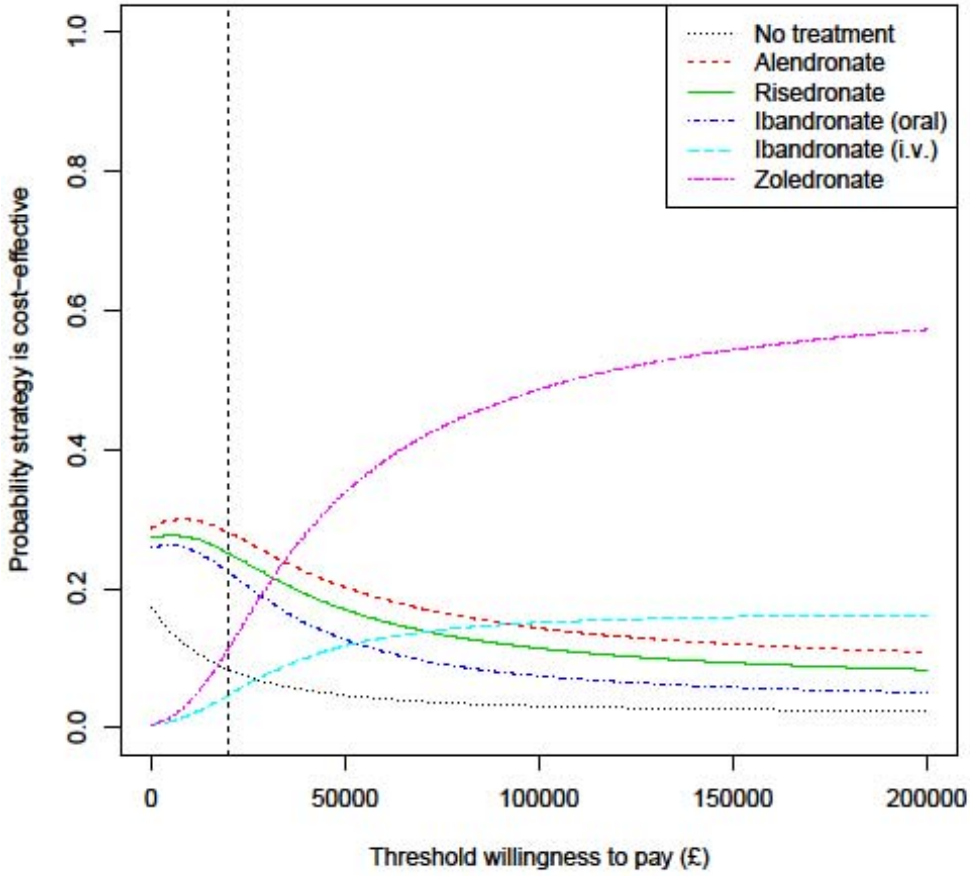


Figure 119 Cost-effectiveness acceptability curve for FRAX risk category 9 (mean absolute risk of 14.9%)

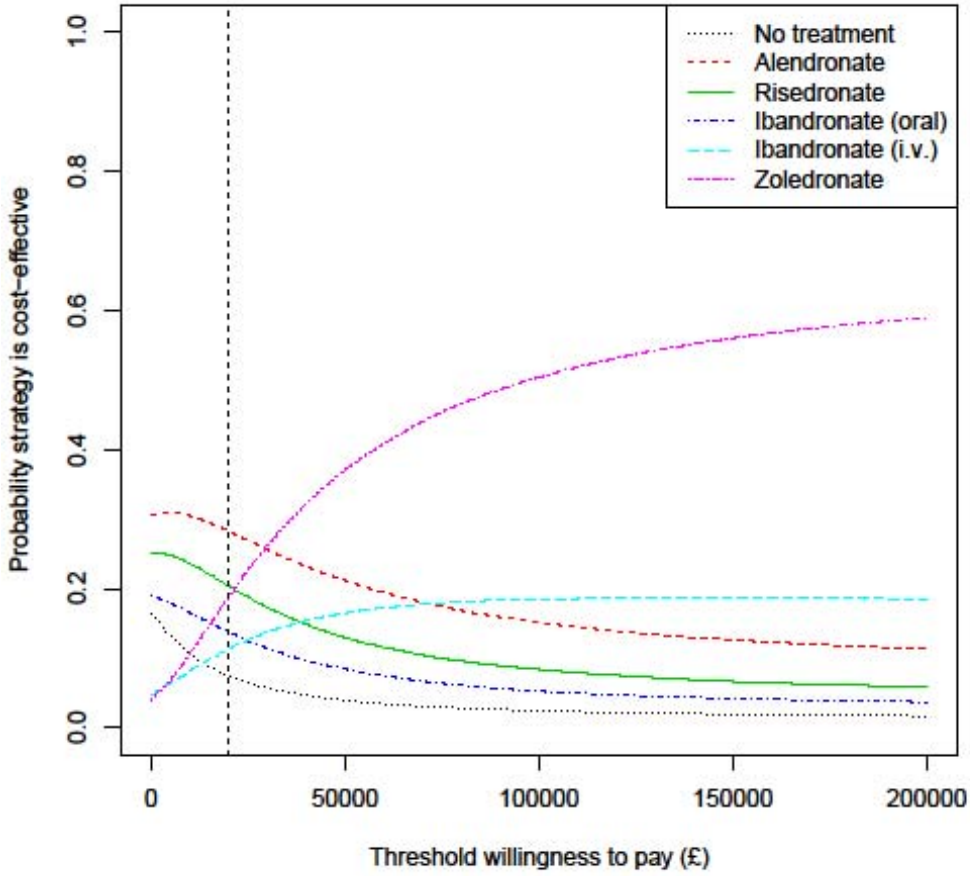
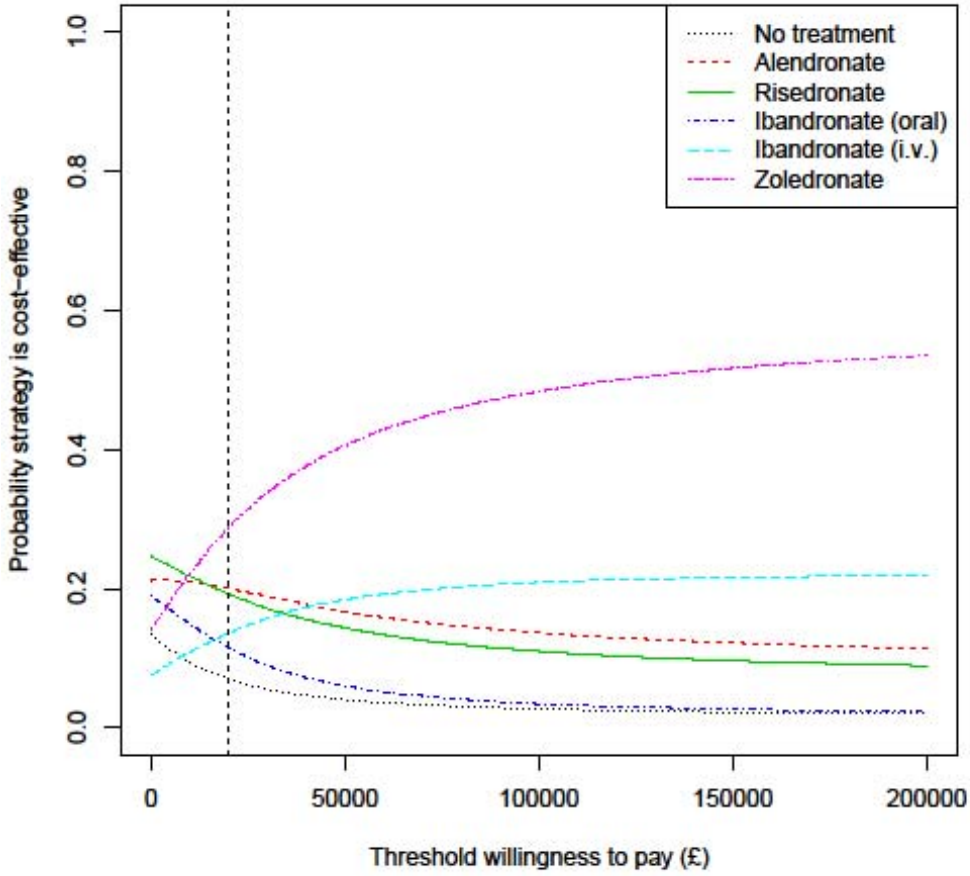


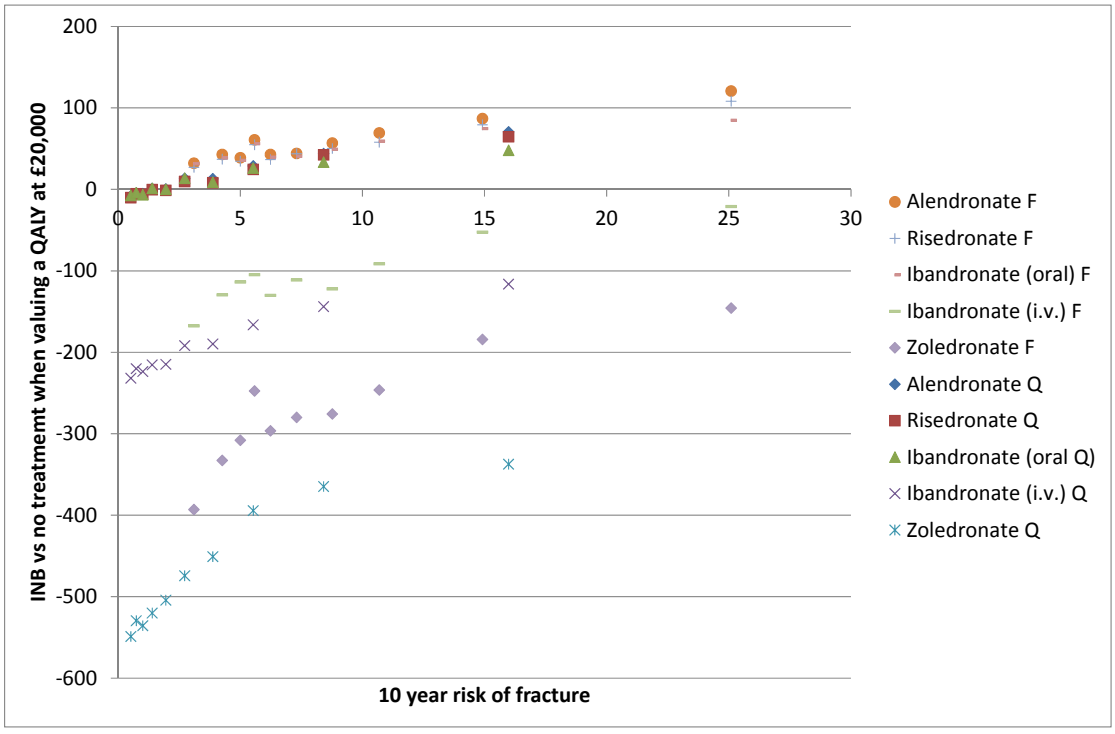
Figure 120 Cost-effectiveness acceptability curve for FRAX risk category 10 (mean absolute risk of 25.1%)



6.2.2.4 Summary cost-effectiveness results for the basecase scenario when using FRAX

Figure 121 summarises the results from the model using midpoint parameter inputs. It shows the incremental net benefit (INB) for each bisphosphonate treatment when compared with no treatment plotted against the 10 year absolute risk of fracture. The "F" and "Q" labels after the drug name indicate where the risk has been predicted by the FRAX and QFracture algorithms respectively. The INB at the various risk levels appear to fall on a slightly higher curve when using FRAX than when using QFracture with the difference being more pronounced for the i.v. bisphosphonates. This behaviour was also observed when examining the PSA results for QFracture and FRAX on the same plot but the difference was slightly less pronounced (data not presented).

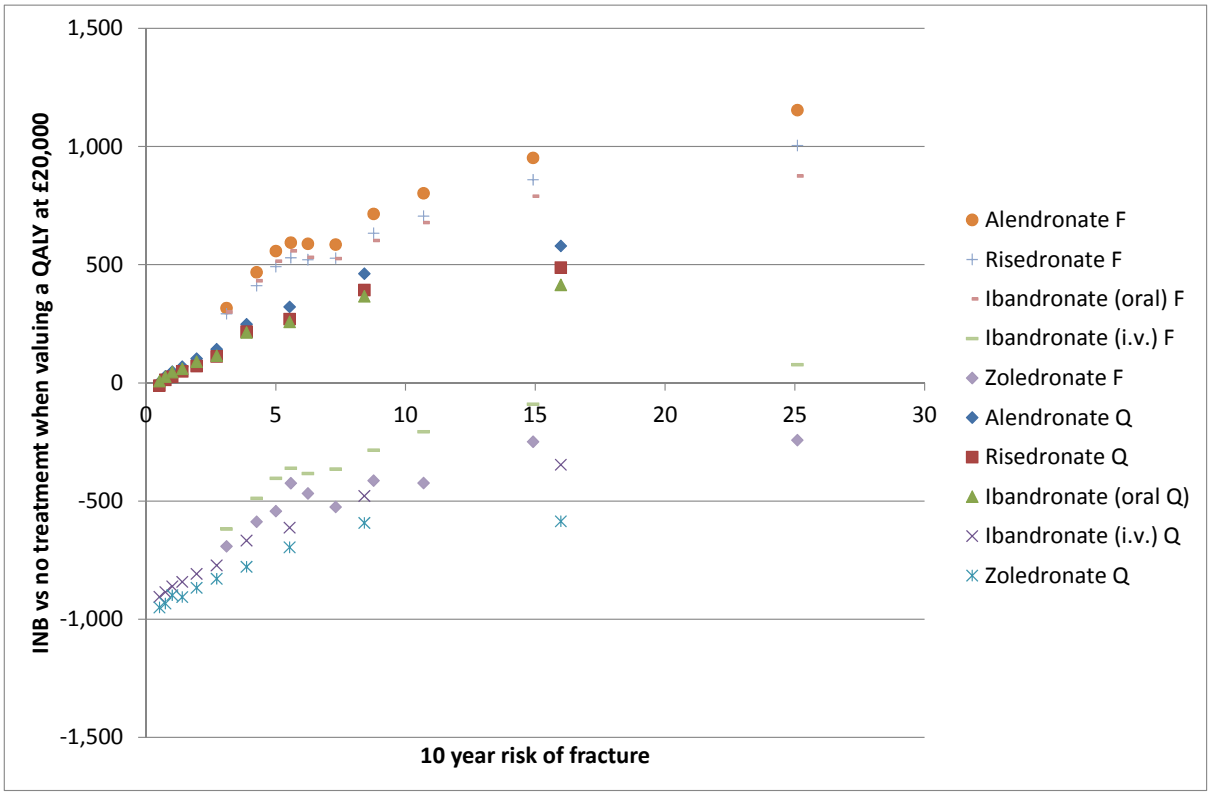
Figure 121 Incremental net benefit (INB) for the basecase scenario when using midpoint parameter estimates



6.2.2.5 Structural sensitivity analyses

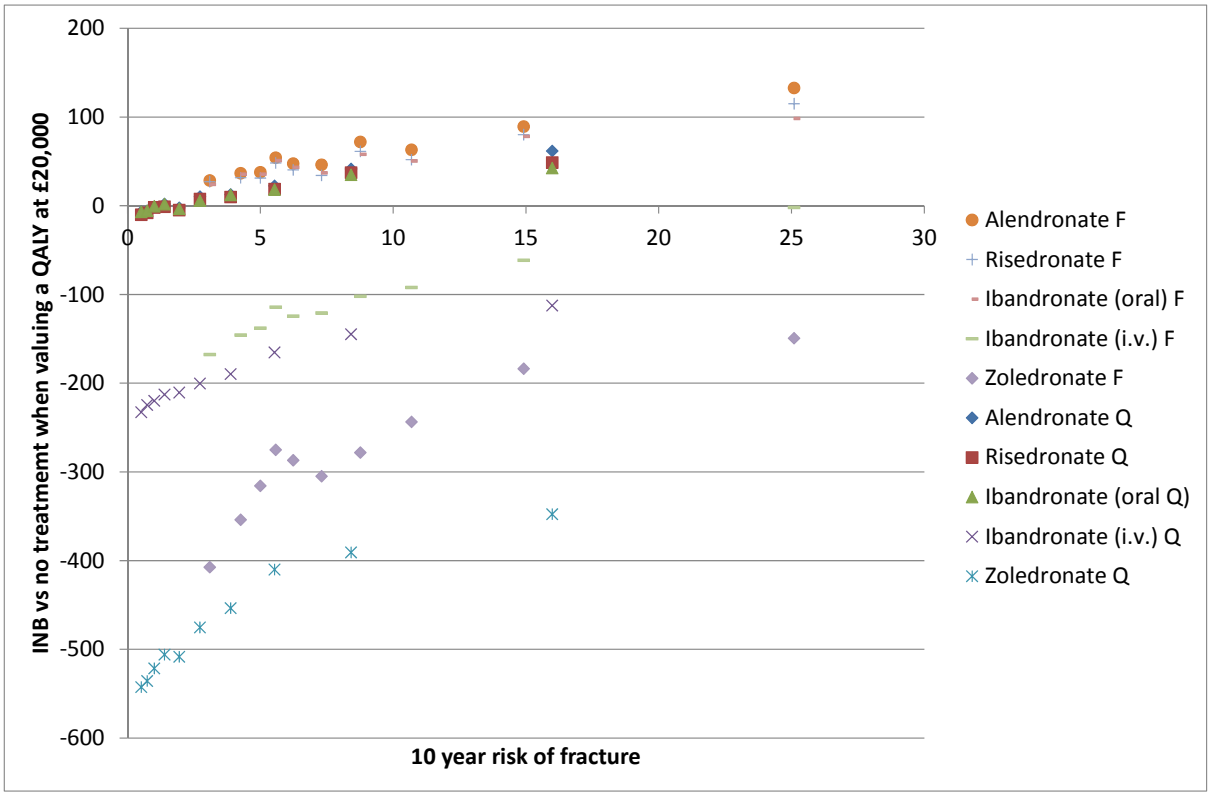
A sensitivity analysis was conducted in which we assumed that all patients would persist with treatment for the intended treatment duration (5 years for oral bisphosphonates and i.v. ibandronate and 3 years for zoledronate). In Figure 122, it can be seen that the INB is positive for oral bisphosphonates in all but the lowest risk category when using QFracture and in all risk categories when using FRAX. This is to be expected because the absolute benefits of treatment are greater when assuming that patients persist with treatment for longer. Therefore as treatment continues the net benefit of treatment outweighs the upfront costs and disutilities associated with adverse events in the first month after initiating treatment. The ICER for i.v. ibandronate versus no treatment falls under £30,000 per QALY in the 8th risk category for FRAX (mean absolute risk of 10.7%) and under £20,000 per QALY in the 10th risk category of FRAX (mean absolute risk of 25.1%). For QFracture the ICER versus no treatment for i.v. ibandronate remains above £30,000 per QALY across all risk categories. For zoledronate the ICER versus no treatment does not fall under £30,000 in any risk category for either FRAX or QFracture.

Figure 122 Incremental net benefit (INB) for the sensitivity analysis assuming full persistence with treatment for 3 years for zoledronate and 5 years for all other bisphosphonate treatments



A sensitivity analysis was conducted in which the rate of admission to a nursing home following hip fracture was applied to both hip and vertebral fractures. The results for this analysis are presented in Figure 123. The results are broadly similar to the basecase results suggesting that our decision not to include nursing home admission following vertebral fracture within the analysis is unlikely to have significantly biased the cost-effectiveness results.

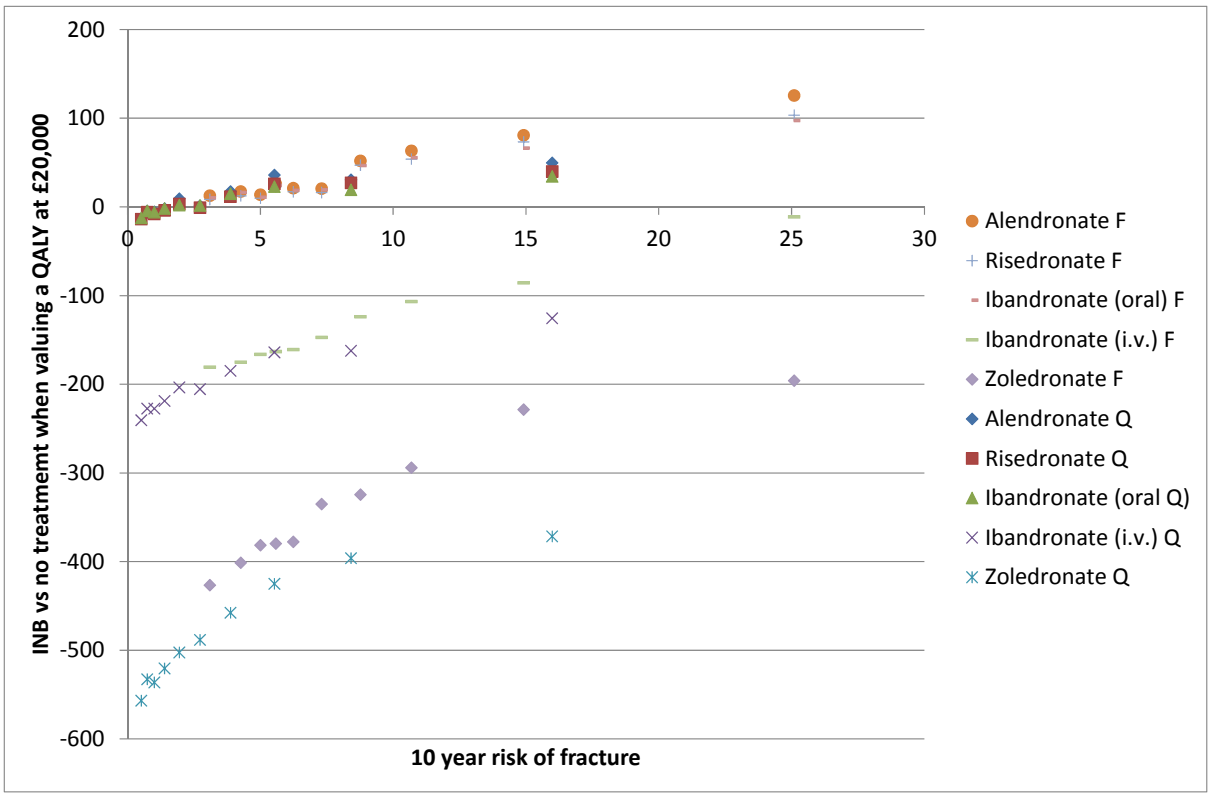
Figure 123: Incremental net benefit (INB) for sensitivity analysis applying nursing home admission rates following hip fracture to vertebral fractures in addition to hip fractures



A sensitivity analysis was conducted in which we removed any fractures occurring at sites other than the four main osteoporotic fracture sites (hip, wrist, proximal humerus and vertebrae). The INBs versus no treatment for both QFracture and FRAX are summarised in Figure 124. It can be seen that the results when using the QFracture algorithm are similar to the basecase but the results when using the FRAX algorithm have a lower INB and are more closely aligned with those for QFracture when considering risk categories with a similar mean absolute risk. The results from this structural sensitivity analysis suggests that the method used to calculate the risks for FRAX from the survival curve for QFracture may have overestimated the absolute risk for FRAX when applying the uplift for additional sites as was

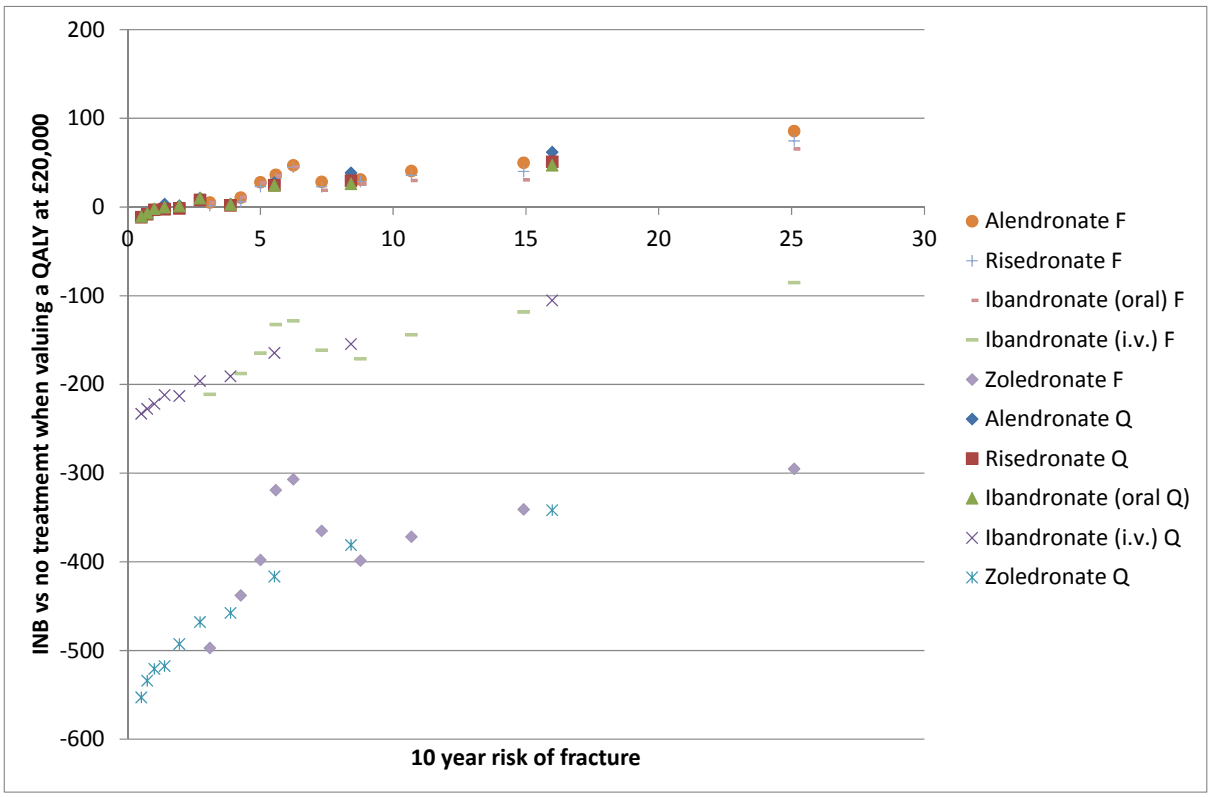
done in the basecase. The basecase results for the FRAX risk categories may therefore be favourable to treatment.

Figure 124 Incremental net benefit (INB) for the sensitivity analysis excluding fractures occurring at sites other than the hip, wrist, proximal humerus and vertebrae.



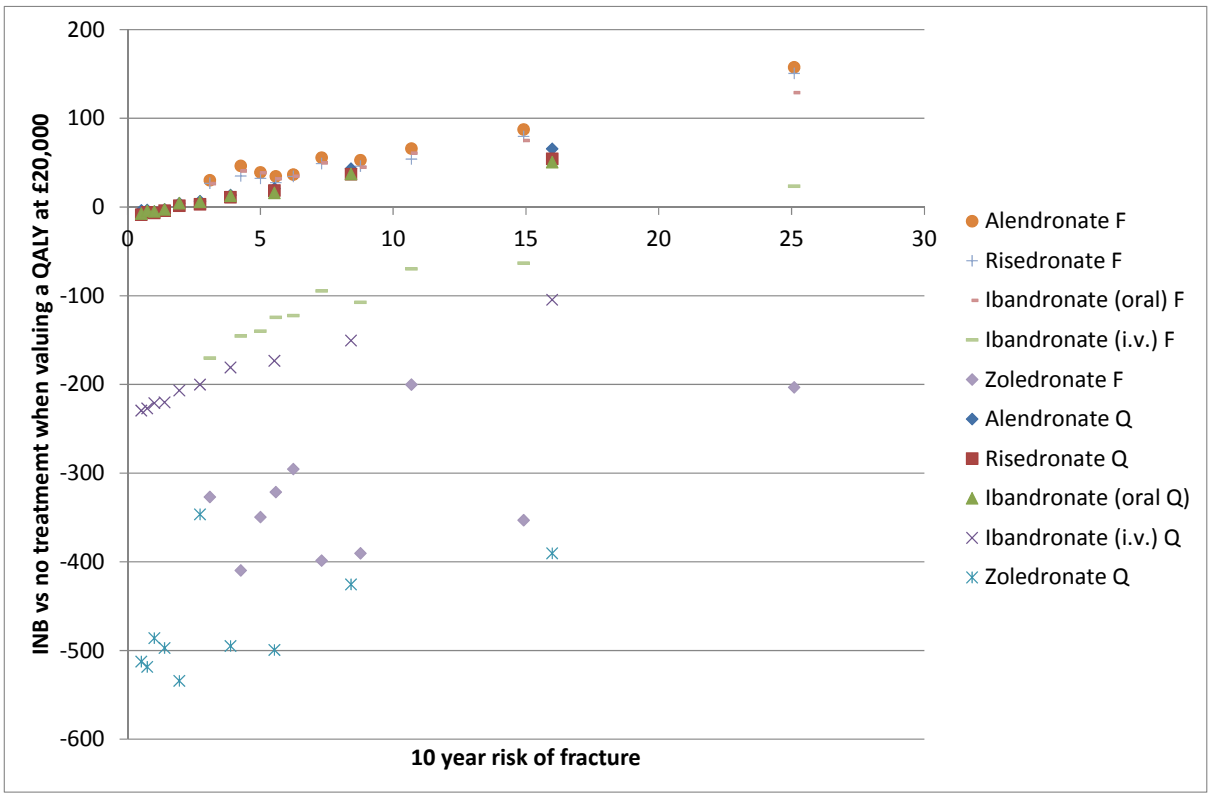
A sensitivity analysis was conducted in which the survival curves for hip fracture were based on the hip specific absolute risk estimates from QFracture rather than a proportion of the absolute risk for the four main osteoporotic fracture sites. The results, shown in Figure 125, are broadly similar to the basecase although the INB estimates for the FRAX risk categories are generally lower and fall closer to those for the QFracture categories with comparable absolute fracture risk. The INBs for all three oral bisphosphonates are negative in the first FRAX risk category (mean absolute risk of 3.1%) and the INB for risedronate is negative in the second FRAX risk category (mean absolute risk of 4.3%). The results of this structural sensitivity analysis suggests that the basecase scenario may have overestimated the cost-effectiveness of treatment for the FRAX risk categories due to the method used to calculate survival curves for FRAX from the data available for QFracture. The cost-effectiveness results for bisphosphonates treatment compared with no treatment may therefore be favourable to treatment when using the FRAX risk scores.

Figure 125 Incremental net benefit (INB) for scenario using hip specific estimates of absolute fracture risk



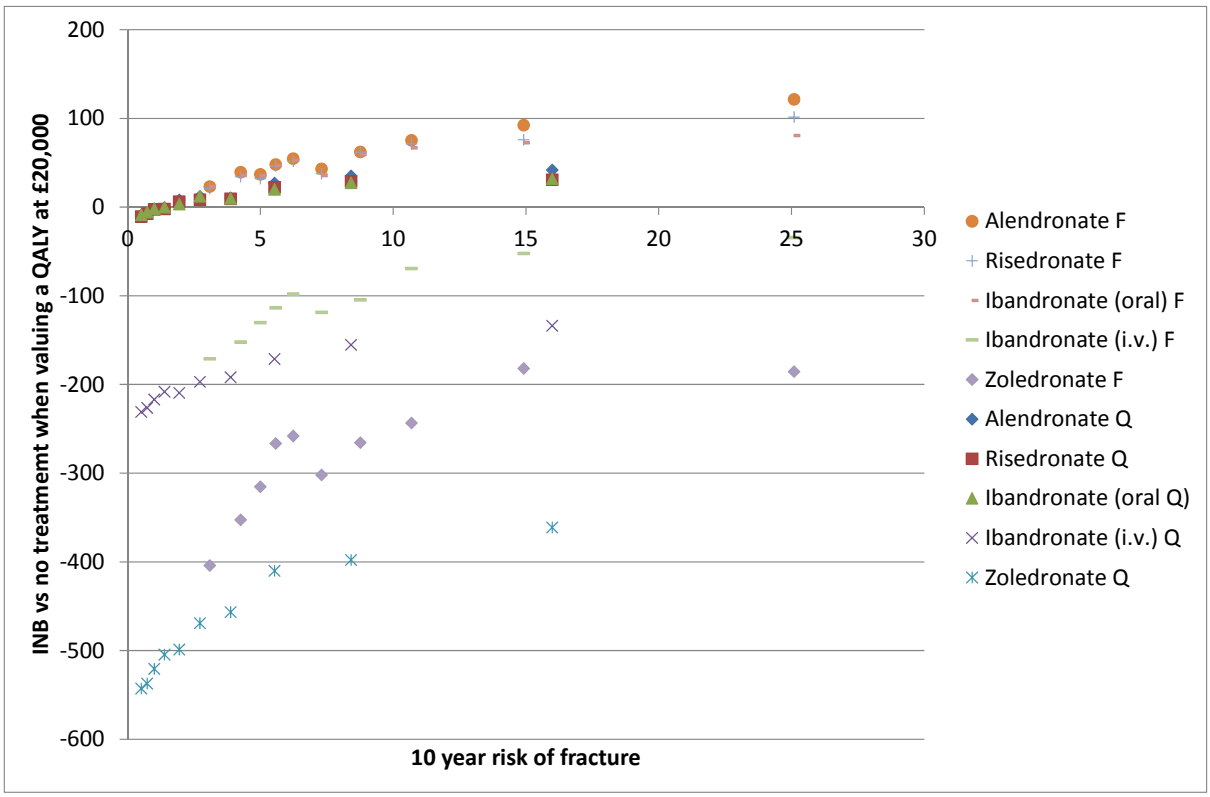
In the analysis assuming full persistence with treatment the duration of treatment for zoledronate was 3 years but the fall-off period was set to 7 years whilst for the other bisphosphonates these durations were 5 years and 5 years respectively. Whilst the assumption ensured that treatment effects fell to zero at 10 years for all drugs, when assuming full persistence, this assumption may have be favourable to zoledronate. In the basecase scenario where mean persistence from observational studies was applied the treatment duration and fall-off period for zoledronate were set to 1.7 years and 4 years (7/3x1.7), respectively. A sensitivity analysis was conducted in which the fall-off period for zoledronate was set equal to the treatment duration (1.7 years for both). The results are summarised in Figure 126. It can be seen that for lower risk categories for QFracture the INB estimates for zoledronate do not vary smoothly suggesting that they have failed to reach a stable estimate probably due to the limited number of fractures prevented when assuming only 1.7 years of treatment and 1.7 years of fall-off time. However, the INB for zoledronate versus no treatment remains below zero for all risk categories for both QFracture and FRAX as was observed in the basecase scenario.

Figure 126 Incremental net benefit (INB) for scenario in which fall-off time was set equal to treatment duration for zoledronate



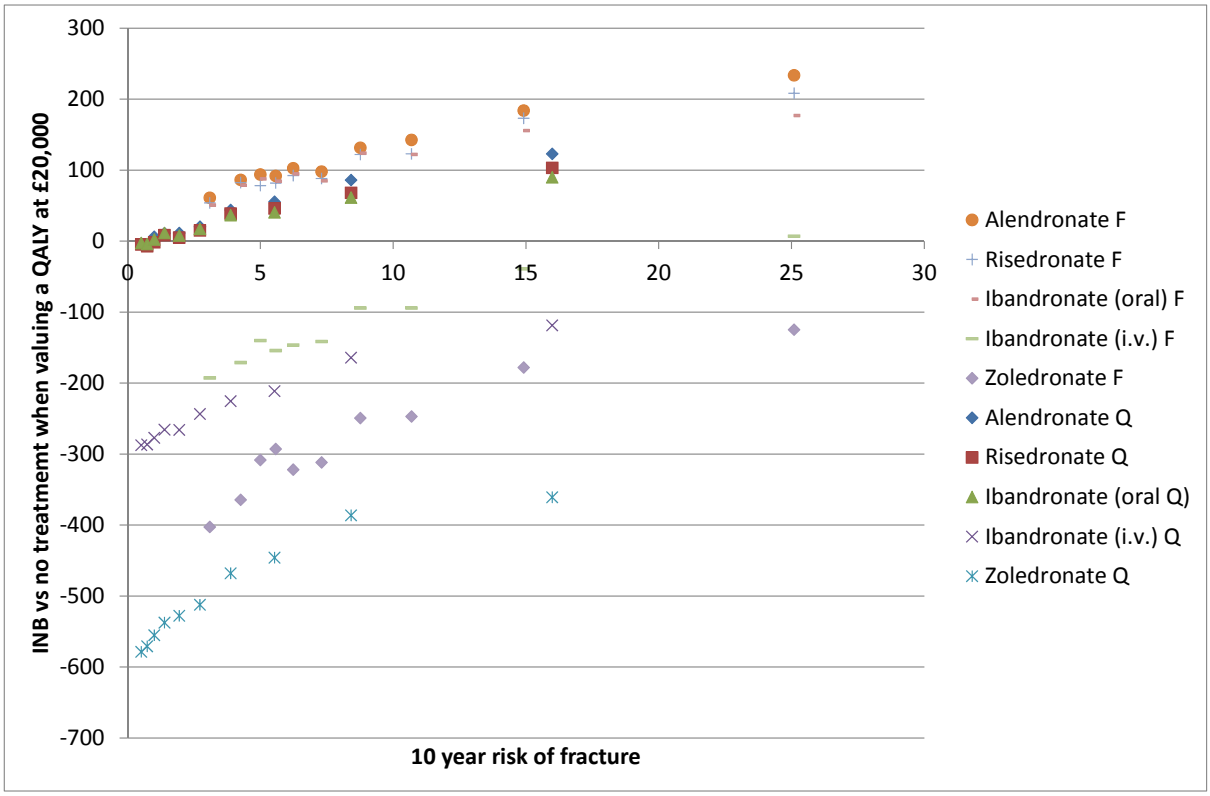
A sensitivity analysis was conducted to examine whether uncertainty regarding the average survival in patients who die following a hip fracture was an important determinant of cost-effectiveness. For this analysis the average duration of survival after hip fracture for hip fractures associated with excess mortality was reduced from 3 months to 1 month. The results, which are summarised in Figure 127, are very close to those seen in the basecase scenario and therefore it can be concluded that the exact duration of survival following a hip fracture associated with excess mortality is not an important determinant of cost-effectiveness.

Figure 127 Incremental net benefit (INB) when assuming that excess mortality associated with hip fractures occurs 1 month after the hip fracture



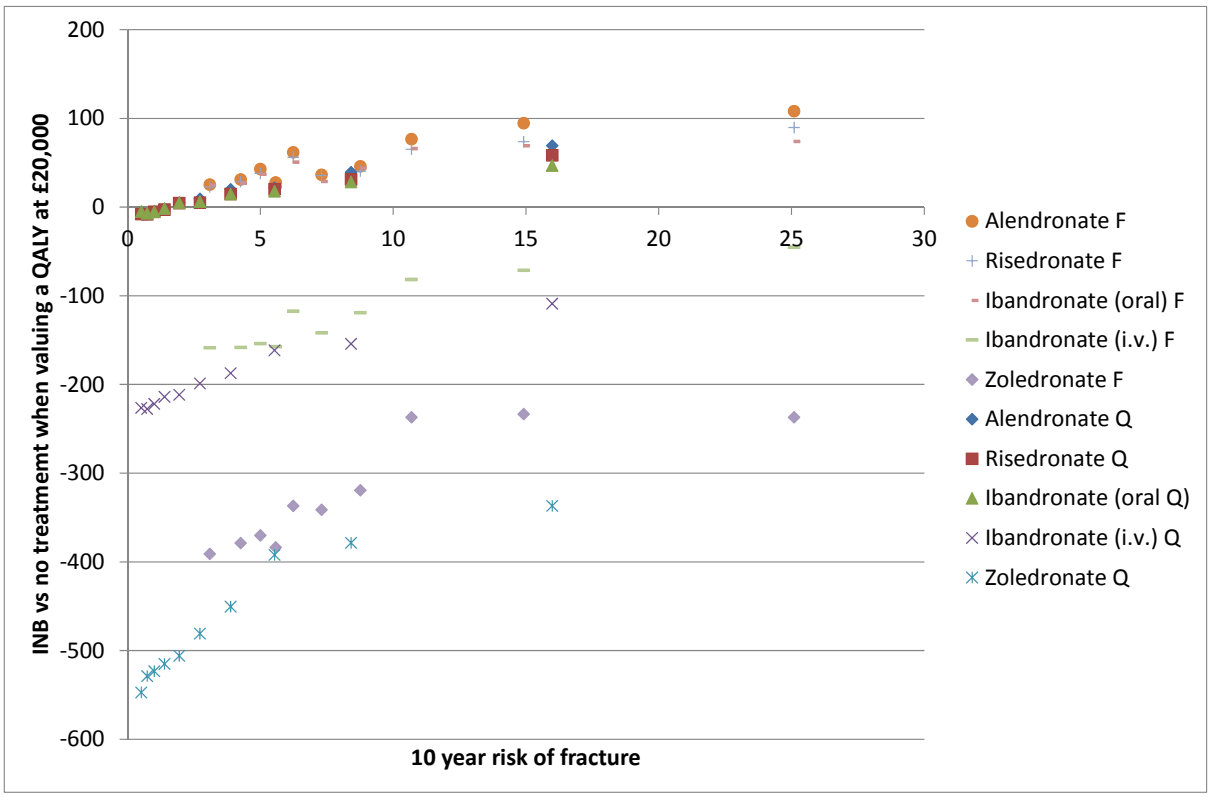
A sensitivity analysis was conducted using the more recent data on the increased risk of fracture following an incident fracture from the systematic review by Warriner *et al.*[231] The results, summarised in Figure 128, show marginally higher INBs for treatment compared to no treatment which is expected because several of the HRs for increased fracture risk following an incident fracture were greater in the paper by Warriner *et al.*[231] than the figures presented in the paper by Klotzbuecher *et al.*[228] which was used in the basecase scenario. However, the results do not appear to be particularly sensitive to the choice of data source for these model parameters.

Figure 128 Incremental net benefit (INB) for sensitivity analysis using Warriner instead of Klotzbuecher as the preferred source for the HR of subsequent fracture following incidence fracture.



A sensitivity analysis was conducted in which the prevalence of a prior fracture at baseline was estimated from UK fracture incidence data rather than using Swedish estimates of the prevalence of a prior fracture. It can be seen from Figure 129 that the results are very similar to the basecase results and therefore the model is not particularly sensitive to the prevalence of a prior fracture at baseline. This may be because a history of prior fracture only has a marginal impact on the individual's utility and health resource use and the increased risk attributed to prior fracture would simply move patients between risk categories rather than making it more or less cost-effective to treat within a particular risk category.

Figure 129 Incremental net benefit (INB) for sensitivity analysis using UK incidence data to estimate the prevalence of prior fracture



In the basecase analysis, data from the 150mg monthly oral ibandronate dosing regimen were applied in the model for the monthly oral dose for all four fracture sites. However, no fracture data were available for the i.v. ibandronate dosing regimen. As this regimen was licensed based on a non-inferiority trial comparing it to the previously licensed 2.5 daily oral dosing regimen, data from the 2.5mg oral dose were applied to the i.v. dosing regimen where these were available. Where these were not available, data from the 150mg monthly oral dosing regimen were applied instead. However, this meant that different data were applied for the oral and i.v. dosing regimen for some fracture sites (vertebral and proximal humerus). A sensitivity analysis was conducted in which the same efficacy data was applied to both the monthly oral and the quarterly i.v. ibandronate dosing regimens. For vertebral and proximal humerus fractures data from the 2.5mg daily oral ibandronate dosing regimen were applied to both as both were licensed based on non-inferiority trials comparing them to the daily 2.5mg oral dose. Data for hip and wrist were unchanged as the only data available were from the 150mg dose and these data were applied to both dosing regimens in the basecase. The efficacy data applied in the basecase and the sensitivity analysis are summarised in Table 38.

Table 38 Hazard ratios (HRs) applied in the basecase and sensitivity analysis for ibandronate treatment regimens

	HRs (median and 95% CrI) applied in the model	
Fracture site	**Monthly oral ibandronate**	**Quarterly i.v. ibandronate**
Basecase		
Hip	0.87 (0.27 - 2.92) from monthly dosing	0.87 (0.27 - 2.92) from monthly dosing
Vertebrae	0.45 (0.21 – 0.96) from monthly dosing	0.47 (0.25 – 0.86) from daily dosing
Proximal humerus	0.80 (0.49 – 1.43) from monthly dosing	0.92 (0.59 – 1.43) from daily dosing
Wrist	0.83 (0.31 – 2.39) from monthly dosing	0.83 (0.31 – 2.39) from monthly dosing
Sensitivity analysis		
Hip	0.87 (0.27 - 2.92) from monthly dosing	0.87 (0.27 - 2.92) from monthly dosing
Vertebrae	0.47 (0.25 – 0.86) from daily dosing	0.47 (0.25 – 0.86) from daily dosing
Proximal humerus	0.92 (0.59 – 1.43) from daily dosing	0.92 (0.59 – 1.43) from daily dosing
Wrist	0.83 (0.31 – 2.39) from monthly dosing	0.83 (0.31 – 2.39) from monthly dosing

The results for this sensitivity are summarised in Figure 130 for the QFracture risk categories and in

Figure **131** for the FRAX risk categories. The estimates presented here are the mean outputs from the PSA which incorporated the joint distribution of the HRs from the NMA. The results are very similar to the basecase analysis suggesting that the model is not particularly sensitive to the choice of data source for the ibandronate HRs. This was to be expected given that the NMA did not find any strong evidence to suggest a difference in efficacy between the monthly and daily dosing ibandronate dosing regimens. It remains possible that there is a difference between fracture outcome for the monthly oral and quarterly i.v. dosing regimens but this could not be assessed within the network meta-analysis because no fracture outcomes were available for the quarterly i.v. dosing regimen.

Figure 130 Incremental net benefit (INB) for sensitivity analysis using same efficacy data for oral and i.v. ibandronate treatments for QFracture risk categories

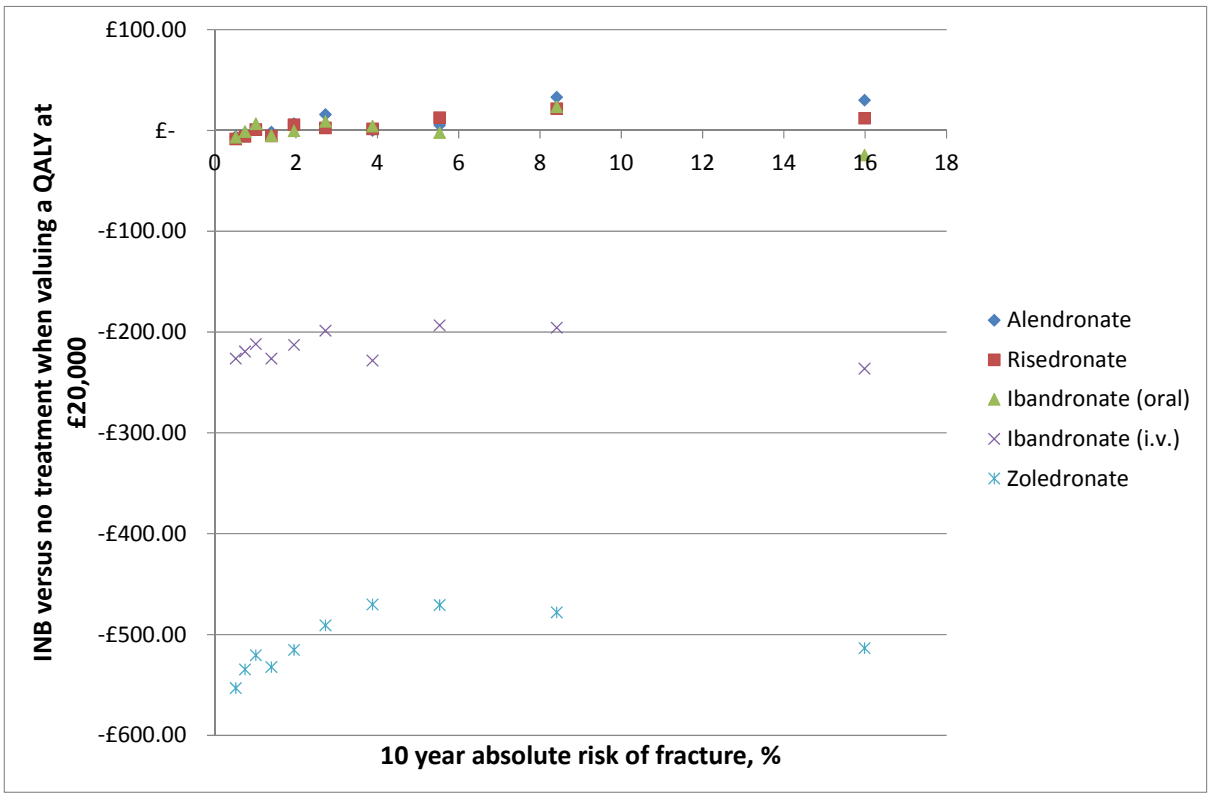
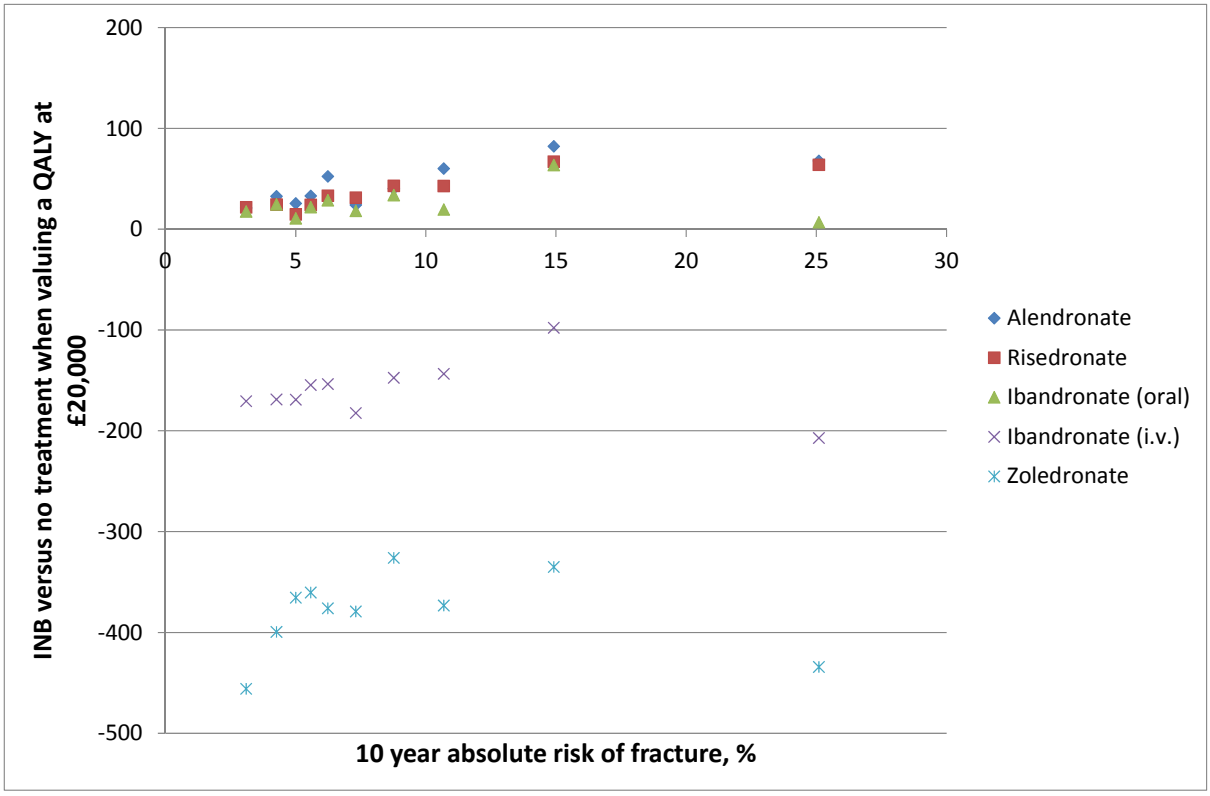


Figure 131 Incremental net benefit (INB) for sensitivity analysis using same efficacy data for oral and i.v. ibandronate treatments for FRAX risk categories



Scenario sensitivity analyses were also conducted on the costs and QALY decrements attributable to adverse events. As AEs were not included as an uncertain parameter in the PSA it was possible to adjust the PSA outputs for different assumptions regarding AEs. Figure 132 and Figure 133 summarise the results when assuming no costs or QALY decrements attributable to AEs for the QFracture and FRAX risk categories respectively. It can be seen that in this scenario the oral bisphosphonates are more cost-effective with only risedronate having a negative INB compared with no treatment in the first QFracture risk decile (mean absolute risk of 0.5%) when valuing a QALY at £20,000. In all other risk categories the oral bisphosphonates have a positive INB except the 5th risk category (mean absolute risk of 2.0%) where only alendronate has a positive INB. However, the results for the i.v. bisphosphonates are similar with negative INBs compared to no treatment across all 10 risk categories for QFracture.

The results across the FRAX risk categories when assuming no costs of QALY decrements attributable to AEs were similar to the basecase scenario with positive INBs for the oral bisphosphonates and negative INBs for the i.v. bisphosphonates when valuing a QALY at either £20,000 or £30,000.

Figure 132 Incremental net benefit (INB) for sensitivity analysis assuming no costs or QALY decrements for adverse side effects for QFracture risk categories

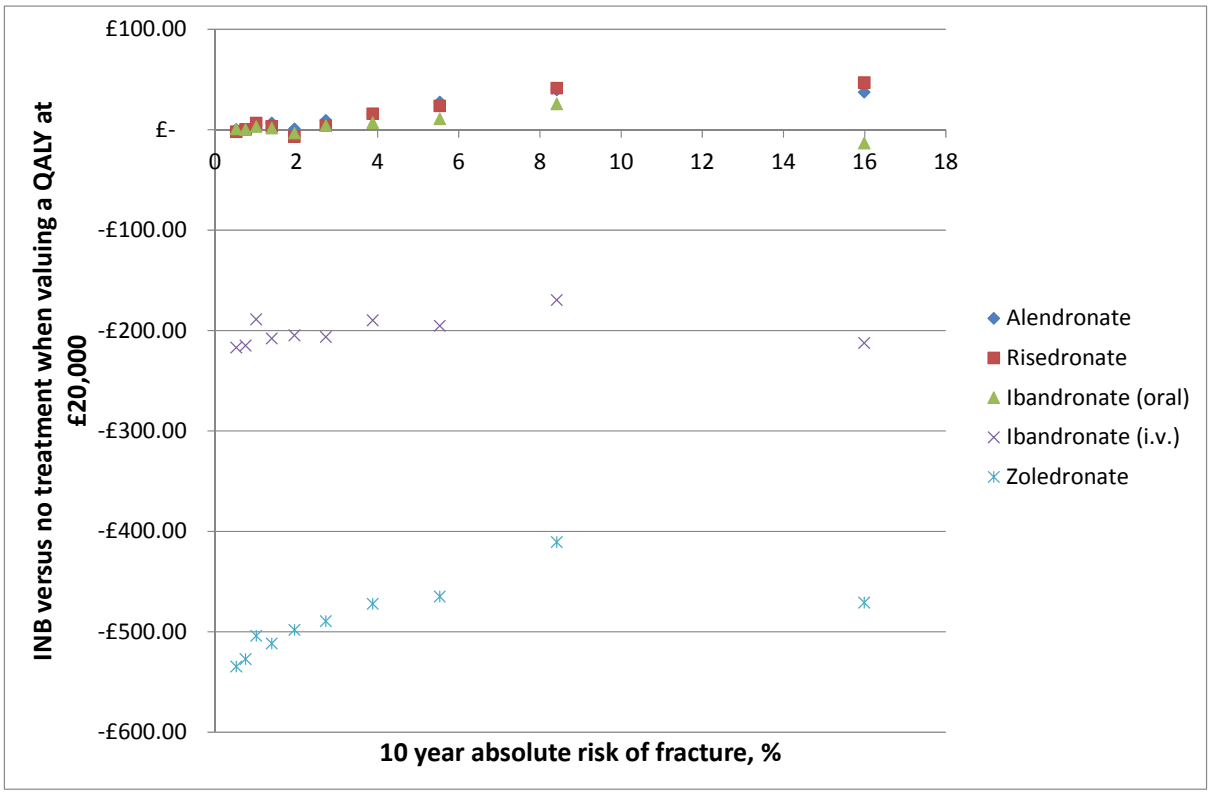
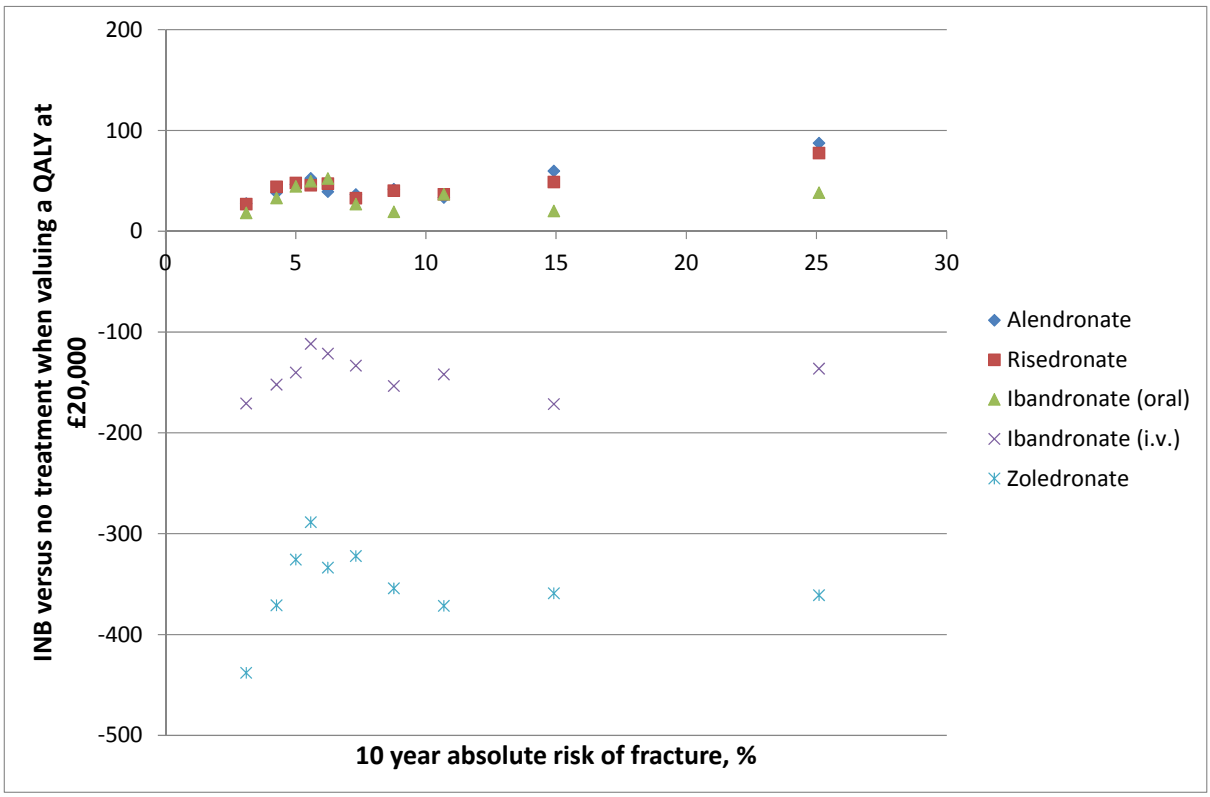


Figure 133 Incremental net benefit (INB) for sensitivity analysis assuming no costs or QALY decrements for adverse side effects for FRAX risk categories



In addition a scenario analysis was conducted in which the rate of adverse side effects for oral bisphosphonates was increased from 3% to 30%. In this scenario none of the oral bisphosphonates had a positive INB compared with no treatment across any of the QFracture risk categories when valuing a QALY at £20,000 as shown in Figure 134. The INBs remained negative for all treatments when valuing a QALY at £30,000 (data not presented).

The results for the FRAX risk categories when assuming an AE rate of 30% for oral bisphosphonates in the first month of treatment are shown in Figure 135. It can be seen that the INB is negative for the three oral bisphosphonates for the first 8 risk categories (mean absolute risk of 10.7% and below), but is positive for alendronate in the 9th FRAX risk category (mean absolute risk of 14.9%) and for all three oral bisphosphonates in the 10th FRAX risk category (mean absolute risk of 25.1%).

Figure 134 Incremental net benefit (INB) for sensitivity analysis assuming a 30% adverse event rate for oral bisphosphonates in the first month of treatment for QFracture risk categories

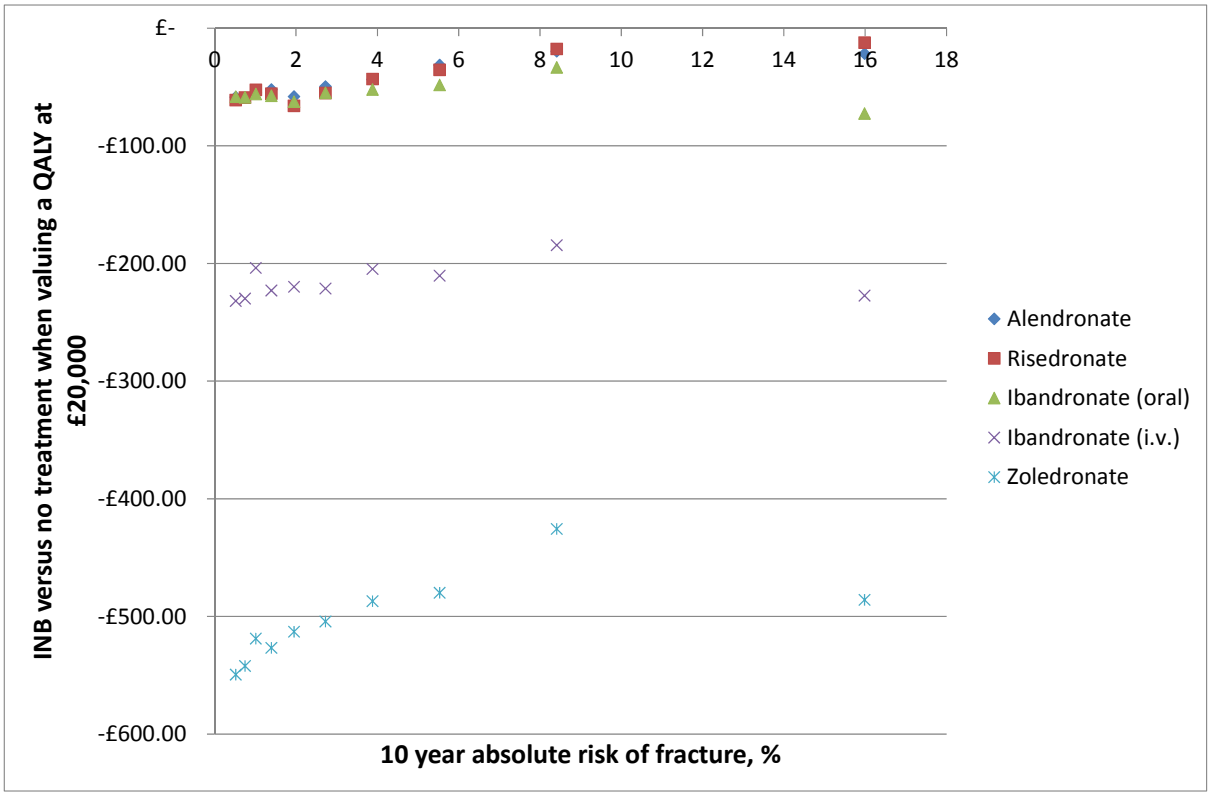
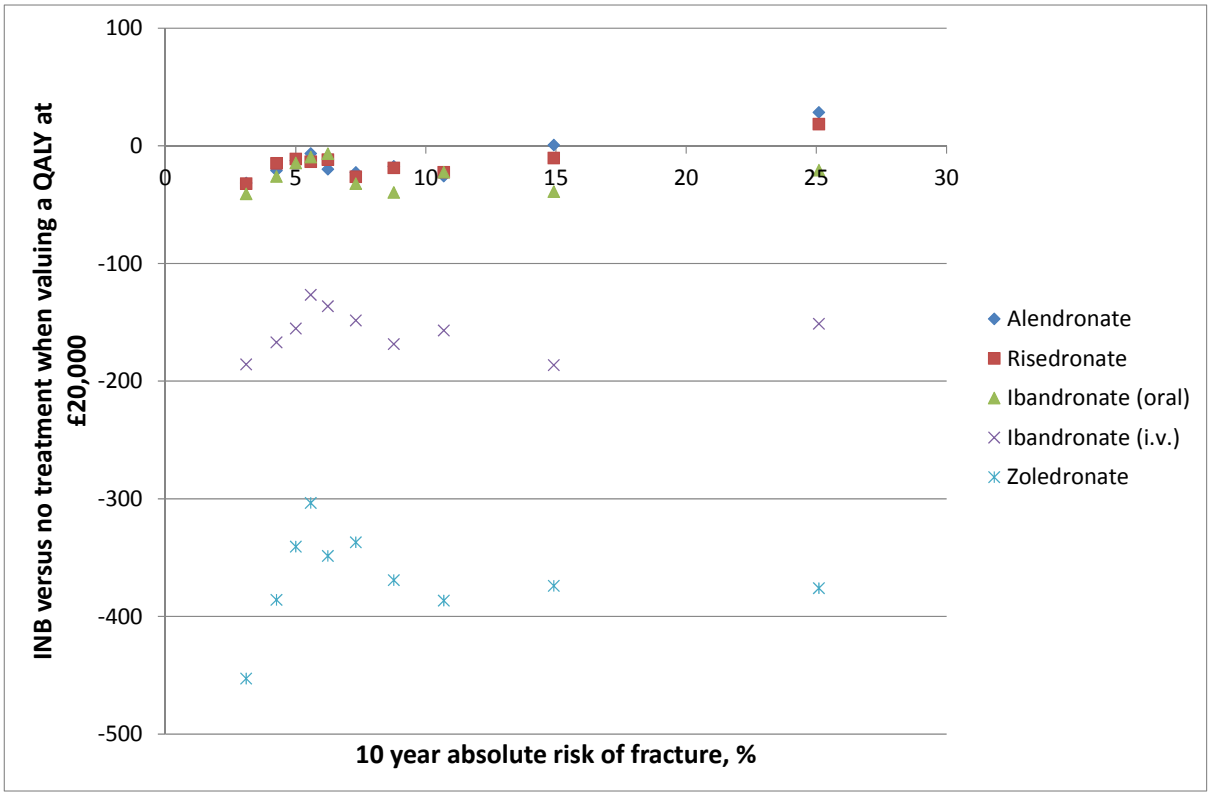


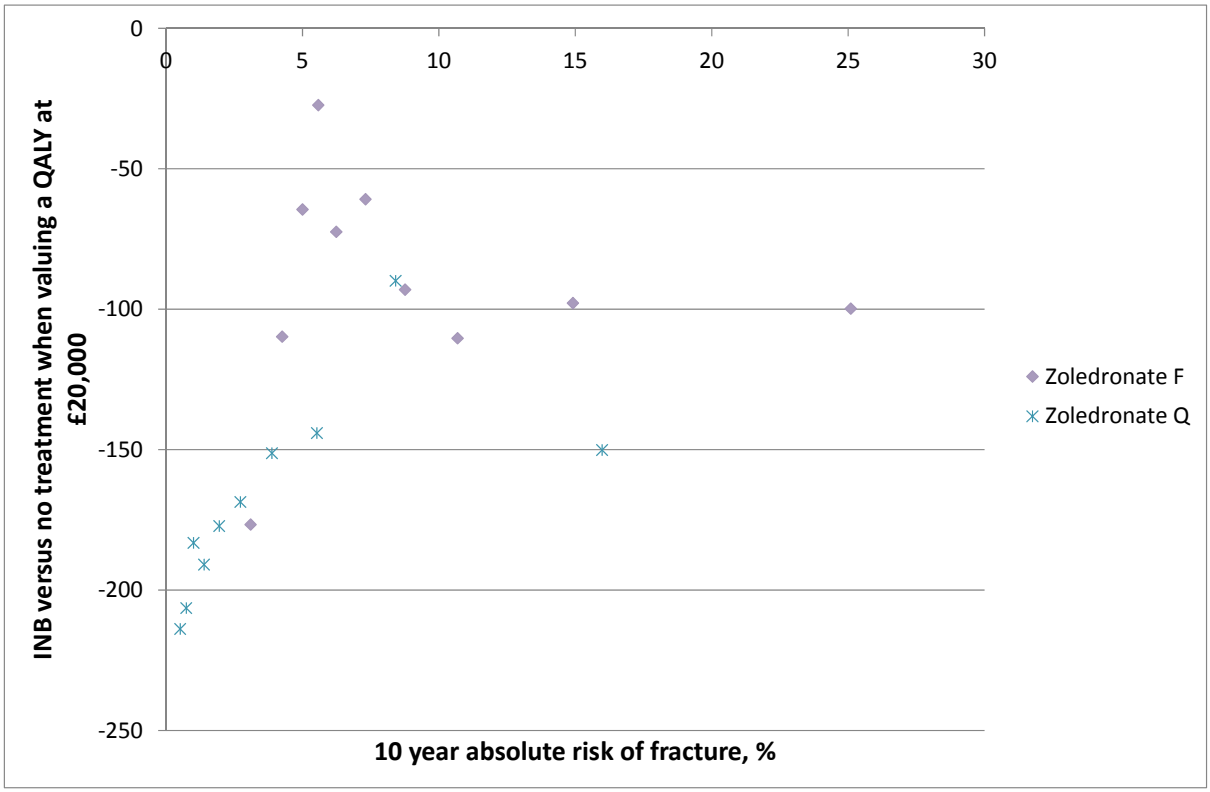
Figure 135 Incremental net benefit (INB) for sensitivity analysis assuming a 30% adverse event rate for oral bisphosphonates in the first month of treatment for FRAX risk categories



Our clinical advisors were concerned that the price of zoledronate, which was taken from the eMIT database, may not be reflective of real world prices due to zoledronate only recently becoming available in a generic format for this indication. We therefore conducted a sensitivity analysis using the price from eMIT for the 4mg dose of generic zoledronate which is licensed for the prevention of skeletal related events in patients with advanced malignancies involving the bone. The average price on eMIT for the most commonly prescribed preparation of zoledronate for this alternative indication was £5.76. It was also noted by clinicians that zoledronate may be administered in some cases as an outpatient procedure rather than as a day case. Therefore we also applied these lower administration costs in addition to the lower drug acquisition cost. This was done using the average outputs from the PSA and by assuming 1.67 doses of zoledronate are administered on average, with the mean number of doses estimated based on 500,000 PSA samples.

The results when assuming these lower costs for zoledronate treatment are summarised in Figure 136 for both QFracture and FRAX. It can be seen that whilst the INB compared with no treatment has increased for zoledronate under these more favourable cost assumptions, the INB is still negative across all 10 risk categories for both QFracture and FRAX.

Figure 136 Incremental net benefit (INB) for zoledronate when assuming a lower acquisition price and outpatient rather than day case administration costs*



*NB: suffix Q indicates results generated using QFracture and suffix F indicates results generated using FRAX

6.2.3 Discussion

In summary, when valuing a QALY at £20,000, a strategy of no treatment is predicted to have the greatest net benefit for patients with a QFracture score of less than 1.5%. Alendronate is predicted to have the maximum net benefit from 1.5% to 7.2% and risedronate is predicted to have the maximum net benefit from 7.2% upwards. However, the absolute costs and QALY gains are small in patients with low absolute risk and there is considerable uncertainty regarding whether no treatment is the optimal strategy until the QFracture score is around 5.5% (the mean absolute risk for the 8th risk category for QFracture).

The mean INBs for oral bisphosphonate treatment compared with no treatment were positive across all FRAX risk categories. However, in the basecase scenario the INBs of bisphosphonate treatments compared with no treatment were generally higher for FRAX than QFracture for risk categories with similar absolute fracture risk. We would expect from the

way the model is structured that the threshold for cost-effective treatment would be broadly similar across the two risk scores. The results of two structural sensitivity analyses suggest that the basecase analysis may have overestimated the fracture risk in the model based on FRAX due to the method used to estimate time to fracture based on the FRAX risk estimates. Given this possible bias in the estimates generated by the model using the FRAX risk score, and our belief that the results should be broadly similar across the two risk scores, it would be reasonable to assume that the absolute risk threshold estimated in the QFracture model could be applied to patients whose score had been calculated using either QFracture or FRAX.

Contrastingly i.v. bisphosphonates had much higher ICERs compared with no treatment. In the highest risk categories the ICERs for i.v. ibandronate and i.v. zoledronate compared with oral bisphosphonates were over £50,000 per QALY even though the basecase analysis assumed longer durations of persistence for i.v. bisphosphonates than oral bisphosphonates. Although the mean INB compared with no treatment for i.v. ibandronate did become positive at very high levels of absolute risk when using QFracture, the results when using FRAX went in the opposite direction. This may be due to the few number of patients and parameter samples informing the estimates at high levels of absolute risk which makes these estimates more uncertain.

The results appeared to be broadly similar when we conducted structural sensitivity analyses examining: applying the risk of nursing home admission following hip fracture to vertebral fractures; shorter duration of survival for hip fractures associated with excess mortality; alternative data source for increased risk of fracture following incident fracture; alternative data source for prevalence of prior fracture at baseline; using the same efficacy estimates for oral and i.v. ibandronate; reducing the acquisition and administration costs for zoledronate; and reducing the fall-off period for zoledronate. For the following sensitivity analyses the results were broadly similar for QFracture but slightly less favourable for FRAX: removing fractures at additional sites from the model; using hip specific absolute risks to estimate time to hip fracture. The results were more favourable to treatment when assuming full persistence with treatment or when assuming no adverse events. The sensitivity analysis examining an adverse event rate of 30% in the month following initiation of oral bisphosphonate therapy showed that the cost-effectiveness of oral bisphosphonate is very sensitive to the rate of adverse events experienced.

The model's estimates of cost-effectiveness are generalizable to patients eligible for risk assessment under CG146 as this is the population we have simulated. However there are some groups with secondary osteoporosis who may be considered eligible for risk assessment under

CG146 who have not been explicitly simulated within our model. Patients at increased risk of fracture after receiving hormone treatments for breast and prostate cancer have not been explicitly simulated although patients with the more general risk factor of 'any cancer' have been included in the simulated cohort. Patients at increased risk of fracture following untreated premature menopause haven't been simulated but the prevalence of hormone replacement therapy (HRT) usage in female patients has been taken into account within the simulated cohort. We might expect the cost-effectiveness in these groups to be similar to groups with other secondary causes of osteoporosis that have been explicitly modelled, such as steroid induced osteoporosis, provided the groups who have not been explicitly modelled have an increased risk of fracture and similar life-expectancy to other causes of secondary osteoporosis which have been modelled.

We have applied all-cause mortality data from the UK general population to the whole modelled cohort. This may overestimate the cost-effectiveness of treating patients who have higher mortality risks due to the presence of comorbidities and therefore the cost-effectiveness estimates may be less generalisable to groups with lower than average life-expectancy.

One of the strengths of the patient-level simulation approach we have used is that we have been able to simulate how the distribution of patient characteristics, such as age, varies between different risk scores and how this influences the cost-effectiveness of treatment. However the patient level simulation approach used required a large number of patients to be simulated due to the sparsity of events in lower risk populations. This made it difficult to accurately measure the incremental costs and QALYs associated with treatment in the lowest risk categories when the treatment durations were reduced to reflect real-world persistence with treatment. However, we were able to use non-parametric regression to estimate the relationship between INB and absolute risk across the whole modelled cohort when averaging over both parameter uncertainty and the stochastic uncertainty associated with patient level simulations. This made it possible to estimate the absolute risk at which the INB crosses zero for each treatment to a more accurate level than could be achieved simply examining the INBs for each risk category.

Fracture risk prediction within the model is based on the risk predicted over time from the QFracture algorithm but when validating the model we identified some internal inconsistencies within QFracture which have implications for our model. The underlying survival function applied in QFracture for patients without any risk factors incorporates a hazard that increases over time. This makes sense as the hazard for fracture is likely to

increase as the patient ages. However, the 1 year risk of fracture predicted for a patient 5 years after their 50th birthday is higher than the 1 year risk of fracture predicted in the following year for a 55 year old. We have assumed that the data points from the earlier years of the QFracture algorithm are likely to be more reliable than points from later years where there may have been fewer patients with follow up in the cohort used to derive the QFracture algorithm. Hippisley-Cox *et al.* report that the 2012 QFracture algorithm was based on approximately 23.6 million patient-years of follow-up in approximately 3.1 million patients suggesting that the mean duration of follow-up was around 7.6 years. We would therefore expect the model predictions to be more robust when used to estimate fracture risk over 5 years than over 10 years.[167] We have therefore re-sampled the patient's fracture risk every time an event occurs and at 5 and 10 years after baseline in all patients. In doing so we have ensured that we have repeatedly sampled from the early part of the survival curve which should be less uncertain as it is based on more patients from the QFracture database. This does however result in some model behaviour which goes against clinical expectations in that the hazard for an individual patient may be lower in the 6th year of the model than in the 4th year despite the increase in the patient's age. Unfortunately there is no way to correct this internal inconsistency whilst using QFracture as the basis for risk prediction within the model. Introducing more frequent events to update risk at annual intervals would minimise the impact of this internal inconsistency but it would significantly reduce the computational efficiency of the model and wouldn't remove the inconsistency altogether. However, this issue is not expected to bias the estimates of cost-effectiveness as it has an equal impact across all treatment strategies.

Several assumptions had to be made to incorporate the FRAX algorithm within the model. Firstly, the FRAX calculator does not provide estimates of the fracture risk for different time periods. Therefore we assumed that the shape of the survival curve for fracture free survival would be similar in FRAX and QFracture and applied a simple ratio to the rate parameter of the QFracture survival curve to generate time to event estimates for the FRAX model. The ratio was calculated to ensure that the time to event estimates for the FRAX model generated a survival curve with the 10 year risk predicted by the FRAX model. Secondly, the FRAX algorithm provides the estimate of fracture risk after taking into account the competing risk of mortality whereas the QFracture algorithm does not incorporate any competing mortality risk. Therefore we may have underestimated the fracture risk in the FRAX model by applying our own competing mortality hazard on top of that incorporated by FRAX. Furthermore, the structural sensitivity analyses conducted on hip fracture risk and the uplift for fractures at additional sites, suggest that the INB of treatment with bisphosphonates compared to a strategy of no treatment may have been overestimated in the basecase due to the method used

to calculate the survival curve for FRAX from the survival curve for QFracture. We suspect that the problem relates to the fact that we did not update the ratio used to adjust the scale parameter at each event which would bias the results if the ratio changes over time. We therefore believe that the results generated using the QFracture algorithm are more robust as we were able to use data from QFracture to directly inform the shape of the fracture free survival curve and to apply all-cause mortality data without underestimating the life-time risk of fracture.

Our population was sampled taking into account the correlation between age and gender and the risk factors of prior fracture, steroid use and nursing home residency. The relationship between age, gender and BMI was also incorporated. However other correlations are likely to exist within the general population which we have not captured. This may mean that the mix of patient characteristics within each decile may not perfectly reflect the mix within each risk category for the population eligible for risk assessment. However, we have tried to capture the correlations between those factors likely to affect risk independently of the absolute risk of fracture as these have the most potential to bias the estimates of cost-effectiveness.

The model doesn't allow for patients to move from community living to an institutional residential setting at any time other than following a fracture which may overestimate the impact of fractures that result in residential care in patients who would have eventually moved into residential care for other reasons. However, the model does allow for patients to live in residential care or to have experienced a prior fracture before being treated with bisphosphonates. This avoids treatment benefits being over-estimated in these groups.

The decision to group fractures occurring at additional sites (scapula, clavicle, sternum, rib, pelvis, humeral shaft and femoral shaft) with one of the four main osteoporotic sites (hip, wrist, proximal humerus, vertebral) may have over or underestimated the impact of fractures at these additional sites if these fractures have different costs and QALY implications from the ones they have been grouped with. However, evidence on the resource use and HRQoL impactions of fractures was focused on the four main fracture sites associated with osteoporosis making it difficult to identify site specific evidence on the consequences of fracture for fractures occurring at other sites.

One of the key limitations of our analysis is that we have assumed that all of the bisphosphonate treatment strategies are viable options for all patients within the population. This allowed us to run the model once for the whole population eligible for risk assessment and to determine a single absolute risk threshold for cost-effective intervention with each

bisphosphonate. Applying a strict interpretation of the licensed indications for each bisphosphonate would have required running the analysis multiple times for different groups who have different treatment options which was not feasible. Whilst incremental analyses are usually conducted over a set of potentially interchangeable treatments, in reality it is often the case that some of the cohort of patients who are eligible for one treatment would be contraindicated for another and allowances are made for this when interpreting the cost-effectiveness results. For example, it is possible to rank the treatments in order of decreasing net benefit and treat with the next most cost-effective treatment when the optimal treatment is contraindicated.

Another limitation of our analysis is that we have assumed equal treatment effectiveness across all patients eligible for risk assessment under CG146. There was no evidence of differential treatment effects with respect to gender and age. However, there was some heterogeneity in treatment effects between studies suggesting differential treatment effects according to study characteristics and the effect of treatment on femoral neck BMD depended on the baseline response.

Our estimates of the costs attributable to fracture don't include the costs of rehabilitation and may therefore underestimate the total cost. They do however, include costs for home help and residential care which fall within the NHS and PSS perspective recommended in the methods guide.[161]

The way in which the DES has been implemented only allows for one acute utility multiplier to be applied at any one time. This may mean that the utility decrement in the year following a severe fracture may be underestimated if another less severe fracture occurs within a year. This may have marginally biased the cost-effectiveness analysis against treatment with bisphosphonates by underestimating the benefits of treatments which prevent hip and vertebral fractures, which have the greatest utility impact in the year following fracture, in populations with a high risk of fractures at other sites. However, two events occurring in the same year is expected to be a rare outcome, particularly in lower risk patients, so any bias is expected to be small.

The model is sensitive to the assumptions regarding adverse events, particularly in the low risk populations where the mean absolute cost savings and QALY gains are small. We have included adverse events for oral bisphosphonates using the rates observed in prescription event monitoring studies. However, no significant difference in upper GI adverse events was found in the placebo controlled RCTs for oral bisphosphonates. It is unclear whether this is

because the RCT population are not representative of the real world population, who may be more likely to experience adverse events, or whether the apparent increased risk in real-world cohorts is confounded by other factors which are controlled for within an RCT.

Our analysis has used the FRAX calculator for patients with unknown BMD as CG146 recommends that patients should only receive a BMD scan if they are close to the treatment threshold and therefore the majority of patients are expected to receive treatment without a BMD scan. FRAX also provides an estimate of fracture risk in patients with known BMD. It is possible that the threshold for cost-effective treatment when using the version of the FRAX calculator developed for patients with known BMD may be slightly different if BMD is correlated with patient characteristics which affect risk independently of BMD. However, to properly ascertain whether the treatment thresholds would be different, we would need information on the relationships between BMD and a range of other risk factors such as age, gender, prior fracture and steroid use. Including BMD within the model without information on these relationships would simply shuffle patients with similar characteristics between the different risk groups. Whilst information is available on the relationship between BMD and some of these risk factors, such as age and BMI,[258] adding additional but incomplete information on the relationship between the various risk factors and BMD may introduce an unintended bias in the estimates of cost-effectiveness. Given that both the QFracture and FRAX algorithm have been developed for use without BMD, the correlations between the risk factors included in these risk sores and BMD is already incorporated within the calculation of fracture risk. Therefore we decided not to run the model using the FRAX algorithm for patients with known BMD.

Whilst the mean INBs for treatment with oral bisphosphonates are positive at low levels of absolute risk, it is important to note that the absolute costs and benefits are small and the no treatment strategy has a reasonable probability of being optimal until the QFracture score is above around 5.5% (the mean absolute risk for the 8th risk category for QFracture). It is therefore possible that patients and clinicians may not consider treatment worthwhile in the lowest risk patients even though it may be cost-effective.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Clinical Guideline 146 provides recommendations for risk assessment for fragility fracture including the use of DXA scans and therefore we have not considered the services required to assess fragility fracture risk prior to offering treatment with bisphosphonates. We do not anticipate that any additional services would be required to offer oral bisphosphonate treatment to the population eligible for risk assessment within CG146 as these treatments are prescribed in primary care. Widespread use of zoledronate or i.v. ibandronate across the population eligible for risk assessment would be likely to result in the requirement for additional capacity in existing services to administer these treatments in secondary care.

We have conducted a simple budget impact analysis to estimate the potential impact on the NHS of changes to current prescribing patterns under certain assumptions. For the purposes of assessing the budget impact we have assumed that bisphosphonate treatment with weekly alendronate is offered to all patients who have a QFracture score above 1.5% but that uptake is gradual with only one fifth of the patients eligible for treatment starting treatment each year over the next 5 years. Alendronate has been chosen as it is neither the cheapest nor the most expensive oral bisphosphonate. The generic weekly alendronate preparation has been assumed to be prescribed in all patients as it both the lowest cost and currently the most commonly prescribed treatment (see Table 1 and Table 2). A QFracture score of 1.5% has been chosen as the threshold for offering treatment as this was the lowest absolute risk at which the INB for any bisphosphonate compared with no treatment was positive when valuing a QALY at £20,000. The economic model simulates a population aged 30 years and above and selects from this population the cohort eligible for risk assessment. It therefore also provides an estimate of the proportion of the general population aged over 30 who would be eligible for risk assessment. The model estimates that for every 100,000 patients who are eligible for risk assessment there are another 63,763 who are not eligible for risk assessment and therefore 61% of the general population are eligible. Combining this with information on the number of people aged over 30 years in England from the ONS (33.7 million)[176] allows the calculation of the number of people eligible for risk assessment (20.6 million). From the characteristics of 200,000 simulated patients we have estimated that 61% of those eligible for risk assessment have a QFracture score above 1.5%. We have assumed that the treatment duration is 6 months as this was the treatment duration applied in the cost-effectiveness model for oral bisphosphonates based on observational data on average persistence with treatment. Using these assumptions, the total undiscounted cost of treating the current prevalent population is estimated to be £95 million over 5 years.

Data from the Prescription Cost Analysis suggest that there are currently 8.3 million prescriptions per annum for oral bisphosphonate treatment in primary care at an estimated cost of £10 million per annum.{Prescribing and Primary Care Team Health and Social Care Information Centre, 2014 1133490 /id} For this cost estimate we applied the cost for generic preparations for each dose to make the figures comparable with those above where generic prescribing was assumed. Over 5 years the undiscounted cost for oral bisphosphonate treatment at the current level of prescribing is estimated to be £50 million.
{Prescribing and Primary Care Team Health and Social Care Information Centre, 2014 1133490 /id}
Therefore we estimate that if all patients with a QFracture score over 1.5% were prescribed oral bisphosphonates, this could double the current cost of bisphosphonate prescribing over the next 5 years. These estimates are provided to give an indication of the maximum cost of additional prescribing with costs likely to be lower if uptake is less than 100%. Costs would also be expected to fall once the prevalent population eligible for treatment have been treated as the numbers becoming eligible for treatment each year will be smaller than the current population who are eligible. Furthermore, some of those whom we have included in the eligible population will already have received bisphosphonate treatment which would further reduce the numbers likely to initiate treatment in the next 5 years. Therefore our estimates provide an upper ceiling on the expected costs.

8. DISCUSSION

8.1 Statement of principle findings

8.1.1 Principal findings – clinical effectiveness

A total of forty-six RCTs were identified that provided data for the clinical effectiveness systematic review. Alendronate was evaluated against placebo in seventeen RCTs. Daily oral ibandronate was evaluated against placebo in three RCTs and against i.v. administration in one RCT. Daily administration of oral ibandronate was evaluated against monthly administration in one RCT. Risedronate was evaluated against placebo in twelve RCTs, and zoledronate was evaluated against placebo in four RCTs. One RCT evaluated alendronate compared with ibandronate, five RCTs evaluated alendronate compared with risedronate, one RCT evaluated zoledronate compared with alendronate, and one RCT evaluated zoledronate compared with risedronate. Maximum trial duration was 48 months.

The risk of bias associated with the included RCTs was assessed using the Cochrane risk of bias instrument. An attrition bias ≥10% across treatment groups was evident for 29 (63%) of the included RCTs. Five trials were reported as either open label or single blind and were considered at high risk of performance bias. Blinded outcome assessment was only reported by 13 (29%) trials.

The outcome measures pre-specified in the final NICE scope were addressed by the included trial evidence to varying degrees. Femoral neck BMD was the most widely reported outcome. Fracture was the second most widely reported outcome. Adverse events were reported by the majority of included trials. Across the included trials there was limited reporting on outcomes of compliance (adherence and persistence), hospitalisation and service use, and quality of life.

A total of 27 RCTs provided suitable fracture data for inclusion in the fracture network meta-analysis: nine evaluating alendronate compared with placebo; three evaluating ibandronate against placebo; nine evaluating risedronate against placebo; three evaluating zoledronate compared with placebo; one evaluating alendronate compared with risedronate; and one evaluating zoledronate compared with risedronate. A total of 35 RCTs provided suitable femoral neck BMD data for inclusion in the BMD network meta-analysis: twelve evaluating alendronate compared with placebo; two evaluating ibandronate compared with placebo; one evaluating ibandronate 2.5 mg per day compared with 3 mg i.v. every three months; one evaluating ibandronate 2.5 mg per day compared with 150 mg per month; ten evaluating risedronate compared with placebo; four evaluating zoledronate compared with placebo; two evaluating alendronate compared with risedronate; one evaluating alendronate compared with

ibandronate; one evaluating risedronate compared with alendronate; and one evaluating zoledronate compared with risedronate.

BMD may be considered as a surrogate for fracture outcomes. Analysis of the femoral neck BMD data was of interest in order to confirm the direction of treatment effects. Since more studies presented data on femoral neck BMD than any of the individual fracture outcome types, the network also provides more information for assessing treatment effect modifiers.

All treatments were associated with beneficial effects on fractures and femoral neck BMD relative to placebo. For vertebral fractures and percentage change in femoral neck BMD the treatment effects were also statistically significant at a conventional 5% level for all treatments. Pairwise comparisons between treatments indicated that no active treatment was statistically significantly more effective than any other active treatment for fracture outcomes. For vertebral fractures and percentage change in femoral neck BMD, the greatest effect was for zoledronate, though in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects. There was no evidence to suggest different treatment effects according to age or gender.

Assessment of vertebral fractures was based on both clinical and morphometric fractures. Ideally the effect of assessment method would be assessed through meta-regression. However, data for clinical fractures were limited. An analysis of the studies reporting clinical fractures did not provide any evidence to suggest differential treatment effects according to assessment method, although the evidence was limited.

The main analyses were based on a class effects model such that the bisphosphonates are assumed to be related but not identical. The treatment effects estimated using the class effects model were broadly similar qualitatively (i.e., direction of effect) and quantitatively (i.e., magnitude of effect) to those estimated using the standard random effects model but with the treatments effects in the class effects model shrunk towards the overall bisphosphonate treatment effect. The qualitative effects of treatment (i.e., direction of effect) were the same for the majority of outcome types and treatments from the class effects and standard random effects models with the exception of zoledronate (hip fractures), ibandronate150 mg per month (hip and wrist fractures) and ibandronate 2.5 mg daily (non-vertebral fractures). Although the point estimates changed from being relative increases in effect in the standard random effects model to relative decreases in effect in the class effects model, there was considerable uncertainty about the true effects as reflect in the credible intervals.

Non-vertebral fractures are used as proxy for fractures of the proximal-humerus, since this outcome is not commonly reported. Two studies presented results for proximal humerus fractures, both considering the effects of risedronate against placebo (VERT-NA, Harris *et al.*, 1999;[72] VERT-MN, Reginster *et al.*, 2000[87]). A random effects meta-analysis of these two studies provided a HR of 0.45 (95% CrI: 0.13, 1.41), which was greater than that estimated for non-vertebral fractures but with considerably more uncertainty.

There were no statistically significant differences between treatments in the incidence of upper gastrointestinal events associated with any oral bisphosphonate compared with placebo when data were pooled across RCTs for each bisphosphonate. However, evidence from one RCT indicated a statistically significant risk of upper GI events in men receiving risedronate compared with placebo. Where reported across the RCTs, treatments were prescribed in accordance with the SmPC for oral bisphosphonates to minimise gastric irritation. There was no evidence of significant differences between treatments in mortality across the RCT evidence when data were pooled by bisphosphonate. However, evidence from one RCT indicated a statistically significant greater proportion of men and women dying following hip fracture who were receiving placebo compared with those receiving zoledronate. There was also no evidence of significant differences between treatments in participants withdrawing due to adverse events across the RCT evidence when data were pooled by bisphosphonate. However, evidence from one RCT indicated a statistically significant greater proportion of men receiving alendronate withdrawing due to adverse events compared with placebo.

In agreement with the SmPC there was evidence of influenza-like symptoms associated with zoledronate. There was no statistically significant difference in the incidence of atrial fibrillation associated with zoledronate compared with placebo (one RCT) or risedronate (one RCT). There was no statistically significant difference in the incidence of bone pain associated with zoledronate compared with placebo (one RCT) or alendronate (one RCT). There was evidence of a statistically significant risk of eye inflammation in the first three days following administration of zoledronate compared with placebo (one RCT). Single RCT evidence indicated no statistically significant difference between zoledronate and placebo in the incidence of stroke over 36 months. All RCTs evaluating zoledronate reported no cases of spontaneous osteonecrosis of the jaw in any treatment group during the trial period.

Adverse events of hypocalcaemia and atypical femoral fracture were not reported outcomes by any RCT of any bisphosphonate.

A summary of evidence from systematic reviews that include observational data indicates that alendronate, risedronate and oral ibandronate have similar rates of GI toxicity when compared with placebo. However, prescription event monitoring study data suggests a high level of reporting of a number of conditions in the first month of therapy with alendronate or risedronate, particularly those affecting the upper gastrointestinal tract. Retrospective cohort data also suggests that switching patients who are stabilized on risedronate to alendronate is associated with an increased risk of GI adverse effects. Zoledronate may be compromised by renal toxicity, and myalgias and arthralgias are evident in the acute phase following i.v. administration. Intravenous bisphosphonates, especially zoledronate, are more likely to predispose patients to osteonecrosis of the jaw. However, in addition to bisphosphonate use, there appear to be several other factors involved in the development of osteonecrosis of the jaw (e.g., dental trauma). There is an increased risk of atypical fracture among bisphosphonate users, however events are rare and long-term bisphosphonate therapy might not be a prerequisite for development of atypical fractures. Moreover, the use of glucocorticoids and proton pump inhibitors are potentially important risk factors for atypical fracture. Bisphosphonates are associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents preclude any definitive conclusions with respect to risk. The review evidence for the use of bisphosphonates and oesophogeal cancer is equivocal.

Evidence for persistence and adherence reported by RCTs was very limited. Where reported, high levels of compliance reported as a pill count were evident over the trial duration. A summary of evidence from systematic reviews including observational data indicates that although patients using weekly bisphosphonate medication follow their prescribed dosing regimens better than those using daily therapy, overall compliance and persistence rates are suboptimal for postmenopausal women receiving bisphosphonate therapy for the treatment of osteoporosis. Furthermore, one third to one half of patients, including men being treated with bisphosphonates for osteoporosis do not take their medication as directed.

With the exception of the RCTs evaluating bisphosphonates in steroid users, the majority of trials included in the clinical effectiveness systematic review typically excluded patients with underlying conditions or receiving medications that affect bone metabolism. Furthermore, patients with history of, or receiving medication for, upper gastrointestinal tract disorders were also excluded by the majority of included trials. Therefore, the effects of alendronate, ibandronate, risedronate and zoledronate are unknown in these populations.

8.1.2 Principal findings – cost-effectiveness

The *de novo* economic model estimates that a strategy of no treatment is predicted to have the greatest net benefit for patients with an absolute risk <1.5% when using QFracture to estimate absolute risk and valuing a QALY at £20,000 . Alendronate is predicted to have the maximum incremental net benefit (INB) from 1.5% to 7.2% and risedronate is predicted to have the maximum INB from 7.2% upwards. However, the absolute costs and QALY gains are small in patients with low absolute risk and the PSA suggested that there is considerable uncertainty regarding whether no treatment is the optimal strategy until the QFracture score is around 5.5% (the mean absolute risk for the 8th risk category for QFracture).

The mean INBs for oral bisphosphonate treatment compared with no treatment were positive across all FRAX risk categories. An exact threshold for the absolute risk at which the INB became positive was therefore not available but the minimum FRAX score in the modelled population was 1.2% and the lowest risk category had a mean absolute risk of 3.1%. Oral ibandronate is predicted to have the highest INB compared with no treatment up to 8.6%, with alendronate having the highest INB from 8.6% to 38.5% and risedronate having the maximum INB above 38.5%. The PSA suggested that there was a low probability of the no treatment strategy being optimal across all FRAX risk categories when valuing a QALY at £20,000. However, the PSA also demonstrated that there is considerable uncertainty regarding the optimal bisphosphonate treatment with all of the oral bisphosphonates having reasonably similar probabilities of having maximum INB across most of the FRAX risk categories.

Contrastingly i.v. bisphosphonates were predicted to have lower INBs than oral bisphosphonates across all levels of absolute risk when estimated using either QFracture or FRAX. In the highest risk categories the ICERs for i.v. ibandronate and i.v. zoledronate compared with oral bisphosphonates were consistently over £50,000 per QALY even though the basecase analysis assumed longer durations of persistence for i.v. bisphosphonates than oral bisphosphonates. Although the mean INB compared with no treatment for i.v. ibandronate did become positive at very high levels of absolute risk when using QFracture, the results when using FRAX went in the opposite direction. This may be due to the few number of patients and parameter samples informing the estimates at high levels of absolute risk which makes these estimates more uncertain.

The results appeared to be broadly similar across the majority of the structural sensitivity analyses which examined the application of alternative data or assumptions. The results were more favourable to treatment when assuming full persistence with treatment for the intended treatment duration (3 years for zoledronate and 5 years for all other bisphosphonates) or when

assuming no adverse events. The sensitivity analysis examining an adverse event rate of 30% in the month following initiation of oral bisphosphonate therapy showed that the cost-effectiveness of oral bisphosphonates is very sensitive to the rate of adverse events experienced. The INBs versus no treatment fell below zero (when valuing a QALY at £20,000) for all ten QFracture risk categories and for all but the highest FRAX risk category when assuming an adverse event rate of 30% in the first month of oral bisphosphonate treatment.

The structural sensitivity analyses which varied the way in which the fracture risk was estimated showed results which were broadly similar for QFracture but slightly less favourable for FRAX which brought the cost-effectiveness estimates from the QFracture and FRAX model closer together for patients with similar mean absolute risk. We would expect from the way the model is structured that the threshold for cost-effective treatment would be broadly similar across the two risk scores but in the basecase scenario the INBs of bisphosphonates compared with no treatment were higher for FRAX than QFracture for risk categories with similar absolute fracture risk. The fact that the results are similar in these particular structural sensitivity analyses suggests that the basecase analysis may have overestimate the fracture risk in the model based on FRAX due to the method used to estimate time to fracture based on the FRAX risk estimates.

8.2 Strengths and limitations of the assessment

The clinical effectiveness systematic review was based on rigorous methods, with comprehensive searches for evidence, a good level of consistency between reviewers in study selection and double checking of data extraction. A formal assessment of methodological quality of included trial was undertaken. Attrition ≥10% across treatment groups was evident for 63% of the included RCTs.

Fracture data were reported for 35 (27%) of the 46 included RCTs and femoral neck BMD data were reported for 35 (76%). However, for fracture there was variability across the included trials in the skeletal fracture site evaluated, the most frequently evaluated being vertebral fracture. In addition, femoral neck BMD was summarised in study reports as the percentage change from baseline, which is a relative measure of treatment effect and tends to have poor statistical properties. Ideally, for a continuous outcome measure assessed at baseline and post-treatment we would work with the post-treatment response adjusted for baseline in an analysis of covariance.

Network meta-analyses were used to synthesise the evidence to permit a coherent comparison of the efficacy of interventions in terms of fracture and femoral neck BMD. An assumption of the model is that the studies are exchangeable in the sense that we would be prepared to treat any patient in the population with all of the treatments. However, not all treatments are licensed in all patient populations which means that the studies are not exchangeable, although the analysis follows the scope defined by NICE.

Adverse event data were also widely reported, and supplemented by review evidence of observational data. However, evidence for compliance and concordance was mainly limited to review evidence of observational data.

Although the search strategy for this assessment report was comprehensive, the possibility of a publication bias cannot be discounted. A formal assessment of publication bias was not undertaken.

The majority of included trials typically excluded patients with underlying conditions or receiving medications that affect bone metabolism. Furthermore, patients with a history of or receiving medication for upper gastrointestinal tract disorders were also excluded by the majority of included trials. Therefore, the effects of alendronate, ibandronate, risedronate and zoledronate are unknown in these populations.

None of the consultee submissions included a *de novo* economic evaluation and none of the published economic evaluations compared all five bisphosphonate treatments specified within the scope of this appraisal in a fully incremental analysis as required by the NICE reference case.

The patient-level simulation approach used in the Assessment Group model allowed the distribution of patient characteristics to differ across the risk categories providing estimates of cost-effectiveness that have taken into account the differing consequences of fracture in patients with different characteristics. However, the DES modelling approach provides a stochastic estimate of the costs and QALYs gained. We therefore needed to simulate a large number of patients to obtain stable estimates of the cost and benefits of treatment. This was particularly true in the lower risks groups in the basecase scenario where we reduced the treatment duration to reflect evidence from observational studies on the duration of persistence with bisphosphonate treatment. In order to obtain stable estimates of the costs and QALYs at differing levels of absolute risk we had to group the patients into broad risk categories. A full incremental analysis has been conducted for each risk category and CEACs

have also been provided allowing the uncertainty in the cost-effectiveness to be assessed at different levels of absolute risk. We have also used a non-parametric regression to estimate the relationship between INB and absolute risk across the whole population eligible for risk assessment in CG146. From this we have identified treatment thresholds for each treatment for both QFracture and FRAX.

The model generally adheres to the NICE's Reference Case and fully addresses the decision problem set out in the final NICE scope. In particular, the modelling approach used allows intervention thresholds to be linked to absolute risk measured using the two risk assessment tools recommended in CG146 as specified in the scope.[23] However, in order to provide a single intervention threshold for each treatment that could be applied across the whole population, we had to assume that all of the bisphosphonate treatment strategies were viable treatment options across all patients eligible for risk assessment within CG146. This would not be true if the licensed indications for each intervention were to be strictly applied.

The *de novo* economic model is underpinned by a network meta-analysis across all drug options which provides a coherent synthesis of the evidence within a single model. Where appropriate and possible, systematic search methods have been used to identify evidence to inform the model's parameters (efficacy evidence and HRQoL). However, it was not feasible to conduct a full systematic review to identify evidence to inform all model parameters and therefore published cost-effectiveness models and published systematic reviews were used to identify appropriate sources of evidence for some model parameters.

8.3 Uncertainties

Although differential effects were found when comparing the bisphosphonates to placebo, and the effects of the bisphosphonates were generally similar, there was uncertainty about the true treatment effects and some evidence of heterogeneity in treatment effects between studies.

It is uncertain whether the cost-effectiveness of bisphosphonate treatment at a particular level of absolute fracture risk would be similar for patients who have been assessed using the FRAX algorithm for patients with known BMD.

8.4 Other relevant factors

Whilst the mean INBs for treatment with oral bisphosphonates are positive at low levels of absolute risk, it is important to note that the absolute costs and benefits are small and the no treatment strategy has a reasonable probability of being optimal until the QFracture score is

above around 5.5% (the mean absolute risk for the 8th risk category for QFracture). It is therefore possible that patients and clinicians may not consider treatment worthwhile in the lowest risk patients even though it may be cost-effective.

9. CONCLUSIONS

All treatments were associated with beneficial effects relative to placebo. For vertebral fractures and percentage change in BMD the treatment effects were also statistically significant for all treatments. For non-vertebral fractures the treatment effects were statistically significant at a conventional 5% level for risedronate, alendronate and zoledronate. For the outcomes of hip fracture and wrist fracture all treatments were associated with beneficial treatment effects relative to placebo, although the treatment effects were not statistically significant at a conventional 5% level. Pairwise comparisons between treatments indicated that no active treatment was significantly more effective than other active treatments for fracture outcomes. For vertebral fractures and percentage change in BMD, the greatest effect was for zoledronate, though in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects.

For the majority of adverse events reported in RCTs no significant difference was found between active treatment and placebo suggesting that bisphosphonates are generally well tolerated in patients enrolled within clinical trials. Prescription event monitoring study data suggests a high level of reporting of a number of conditions in the first month of therapy with alendronate or risedronate, particularly those affecting the upper gastrointestinal tract suggesting that oral bisphosphonates may be less well tolerated in clinical practice. A significant difference in the incidence of influenza-like symptoms was identified from the RCTs for zoledronate compared with placebo, although clinical advice was that these symptoms are generally limited to the first dose and usually last only a few days.

The *de novo* economic model estimates that when using QFracture to estimate absolute risk, a strategy of no treatment is predicted to have the greatest net benefit, when valuing a QALY at £20,000, in the lowest risk patients (QFracture absolute risk <1.5%), with oral bisphosphonates having the greatest INB at higher levels of absolute risk. However, the absolute costs and QALY gains are small in patients with low absolute risk and the PSA suggested that there is considerable uncertainty regarding whether no treatment is the optimal strategy until the QFracture score is around 5.5% (the mean absolute risk for the 8th risk category for QFracture).

The mean INBs compared with no treatment (when valuing a QALY at £20,000) were positive for all oral bisphosphonate treatments across all FRAX risk categories. However, in the basecase scenario the INBs of bisphosphonate treatments compared with no treatment were generally higher for FRAX than QFracture for risk categories with similar absolute

fracture risk. We would expect from the way the model is structured that the threshold for cost-effective treatment would be broadly similar across the two risk scores. The results of two structural sensitivity analyses suggest that the because analysis may have overestimated the fracture risk in the model based on FRAX due to the method used to estimate time to fracture from the FRAX absolute risk estimates. Given this possible bias in the estimates generated by the model using the FRAX absolute risk estimates, and our belief that the results should be broadly similar across the two risk scores, it would be reasonable to assume that the absolute risk thresholds estimated in the QFracture model could be applied to patients whose score had been calculated using either QFracture or FRAX.

The *de novo* economic model suggests that the cost-effectiveness of i.v. bisphosphonates is less favourable than for oral bisphosphonates with a negative INB (when valuing a QALY at £20,000) compared with no treatment estimated for both i.v. bisphosphonates across all ten risk categories for both FRAX and QFracture.

9.1 Implications for service provision

The prescribing of oral bisphosphonates in patients who have already received risk assessment under CG146 is not anticipated to have any major implications for service provision as these can be prescribed in primary care. If i.v. bisphosphonates were to be widely prescribed across the population eligible for risk assessment under CG 146, it is likely that additional capacity would be required in existing services to administer these treatment in secondary care.

9.2 Suggested research priorities

Given that the cost-effectiveness results are sensitive to the assumptions regarding the rate of adverse events for oral bisphosphonates, further research to quantify both the incidence of adverse events and the impact of those adverse events on HRQoL and treatment persistence would allow patients and clinicians to make better informed decisions regarding the balance of costs, benefits and adverse effects.

We identified only a limited number of RCTs in men. There was evidence from single RCTs in men which showed a significant increase in upper GI adverse events and withdrawals due to adverse events compared with placebo. Further research to assess efficacy and tolerability of bisphosphonate treatment in men may be beneficial.

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11. APPENDICES

Appendix 1: Protocol

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

Final Protocol 4 September 2014

1. Title of the project:

Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161)

2. Name of TAR team and 'lead'

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3. Plain English Summary

Osteoporosis is a disease characterised by low bone mass (BMD) and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (a broken bone resulting from a fall at standing height or less). Fractures cause significant pain, disability and loss of independence and can be fatal.[1] Osteoporosis affects over three million people in the UK.[2] The UK has one of the highest rates of fracture in Europe, every year 300,000 people in the UK suffer a fragility fracture, including over 70,000 hip fractures.[3] In the UK, 1,150 people die every month following a hip fracture.[4] In 2002 the cost to the National Health Service per annum was estimated to be £1.7 billion, with the potential to increase to £2.1 billion by 2020, as estimated in 2005.[5] Whilst osteoporosis is an important predictor of the risk of fragility fracture, 70% of fragility fractures in postmenopausal women occur in those who do not meet the criteria for osteoporosis.[6]

4. Decision problem

4.1 Purpose of the decision to be made

This assessment will address the question "what is the clinical effectiveness and cost-effectiveness of alendronate, ibandronate, risedronate and zoledronate in the prevention of fragility fractures as compared against each other or a non-active treatment?"

4.2 Clear definition of interventions

Four interventions will be considered within this assessment: alendronate, ibandronate, risedronate and zoledronate which are nitrogenous bisphosphonates. Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.[7]

(1) Alendronate (Fosamax, Fosamax Once Weekly and Fosavance [co-formulation with cholecalciferol], MSD) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once daily or weekly. It also has a UK marketing authorisation for treating osteoporosis in men and for preventing and treating glucocorticoid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy, orally once daily.[8]

Non-proprietary alendronate (AAH, Accord, Actavis, Alliance Healthcare, Almus, Apotex UK, Fannin UK, Focus, Generics UK, Kent, Mylan UK, Phoenix Healthcare Distribution, PLIVA, Ranbaxy, Rosemont, Somex, Sun, Teva UK, Waymade, Wockhardt and Zentiva) also has a UK marketing authorisation for the same indications.[8]

Alendronate in the treatment of postmenopausal osteoporosis is administered orally 10 mg daily or 70 mg once weekly. Treatment of osteoporosis in men is 10 mg daily. Prevention and treatment of glucocorticoid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy is 10 mg daily. Treatment is administered while sitting or standing and patients should remain seated or stood for at least 30 minutes.[7]

(2) Ibandronate (Boniva, Roche) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once monthly or every 3 months by intravenous injection. Non-proprietary ibandronate (Actavis UK, Consilient Health, Mylan UK, Sun and Teva UK) also has a UK marketing authorisation for the same indications[8].

Ibandronate in the treatment of postmenopausal osteoporosis is administered either by mouth 150 mg once a month or by intravenous injection over 15–30 seconds, 3 mg every 3 months. Oral treatment is administered while sitting or standing and patients should remain seated or stood for at least one hour.[7]

(3) Risedronate (Actonel and Actonel Once a Week, Warner Chilcott) has a UK marketing authorisation for treating postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, orally once daily or weekly. It has a marketing authorisation for preventing osteoporosis (including glucocorticoid-induced osteoporosis) in postmenopausal women, orally once daily, and for treating osteoporosis in men at high risk of fractures, orally once weekly. Non-proprietary risedronate (AAH, Actavis, Alliance Healthcare, Aspire, Aurobindo, Bluefish, Dr Reddy's Laboratories, Mylan UK, Phoenix Healthcare Distribution, Ranbaxy, Sandoz, Sovereign Medical, Teva UK, and Zentiva) also has a UK marketing authorisation for the same indications[8].

Risedronate in the treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures is administered 5 mg daily or 35 mg once weekly. For the prevention of osteoporosis (including glucocorticoid-induced osteoporosis) in postmenopausal women, administration is 5 mg daily. Treatment of osteoporosis in men at high risk of fractures is 35 mg once weekly. Patients should remain seated or stood for at least one hour after administration.[7]

(4) Zoledronate (Aclasta, Novartis) has a UK marketing authorisation for treating postmenopausal osteoporosis and osteoporosis in men (including glucocorticoid-induced osteoporosis in postmenopausal women and men) by intravenous infusion once a year. Zoledronate in the treatment of postmenopausal osteoporosis and osteoporosis in men (including glucocorticoid-induced osteoporosis in men and postmenopausal women) is administered by intravenous infusion, 5 mg over at least 15 minutes once a year. In patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair.[7] Non-proprietary zoledronate (SUN Pharmaceuticals and Dr Reddy's) also has a UK marketing authorisation for the same indications.[9]

4.3 Place of the intervention in the treatment pathway(s)

Currently, related NICE guidance includes a clinical guideline for identifying women and men at risk of fracture [1] and three technology appraisals[22,24,30] of treatments for post-menopausal women only.

NICE technology appraisal guidance 160 (Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women),[10] recommends alendronate as first-line treatment for the primary prevention of fragility fractures in postmenopausal women with osteoporosis who have an increased fracture risk defined by age, T-score, and number of independent clinical risk factors for fracture, or indicators of low BMD. For women who cannot take alendronate, NICE technology appraisal guidance 160[10] and 204 (Denosumab for the prevention of

osteoporotic fractures in postmenopausal women),[11] recommends risedronate, etidronate, strontium ranelate, teriparatide or denosumab, at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[8]

NICE technology appraisal guidance 161 (secondary prevention, in women who have already sustained a fracture), [12] recommends alendronate for secondary prevention of fragility fractures in post-menopausal women with confirmed osteoporosis. For women who cannot take alendronate, NICE technology appraisal guidance 161[12] recommends risedronate, etidronate, raloxifene, strontium ranelate, and teriparatide at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.[8]

NICE technology appraisal guidance 204[11] recommends denosumab as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.[8]

People with osteoporosis who cannot tolerate oral therapies should be referred to secondary care for consideration of intravenous zoledronate or subcutaneous denosumab.

4.4 Relevant comparators

Bisphosphonates (alendronate, ibandronate, risedronate and zoledronate) may be compared against each other or a non-active agent, e.g., placebo.

Other bisphosphonates (e.g., etidronate) and other active agents (e.g., raloxifene, strontium ranelate, and teriparatide) will not be considered as comparators in this assessment.

Etidronate is not included as a comparator as it has been discontinued by the manufacturer in the UK. Non-bisphosphonates licensed for the prevention of fragility fractures in women and men will be considered in a separate MTA once this MTA on bisphosphonates has published its final appraisal determination

4.5 Population and relevant sub-groups

The assessment will consider adults assessed for risk of fragility fracture, according to the recommendations in NICE clinical guideline 146 as follows:

(1) All women aged 65 years and over.

(2) All men aged 75 years and over.

(3) Women aged 64 years and under in the presence of risk factors, for example:

- low BMD (a T-score of -1 standard deviations (SD) or more below the young adult mean) previously measured by DXA at the femoral hip,
- previous fragility fracture,
- current use or frequent recent use of oral or systemic glucocorticoids,
- history of falls,
- family history of hip fracture,
- other causes of secondary osteoporosis,
- low body mass index (BMI) (less than 18.5 kg/m^2),
- smoking,
- alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

(4) Men aged 74 years and under in the presence of risk factors (as specified in (3) for women aged 64 years and under).

4.6 Key factors to be addressed

The objectives of the assessment are to:

- evaluate the clinical effectiveness of each intervention
- evaluate the adverse effect profile of each intervention
- evaluate the incremental cost-effectiveness of each intervention compared against (i) each other and (ii) no active treatment
- estimate the overall NHS budget impact in England and Wales

4.7 Factors that are outside the scope of the appraisal

An evaluation of the interventions in the following populations is outside of the appraisal scope and will not be considered in this assessment:

- Women aged 64 years and under without a risk factor (as listed under 4.5)
- Men aged 74 years and under without a risk factor (as listed under 4.5)

5. Methods for the synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'[13] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[14]

5.1. Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature relating to alendronate, ibandronate, risedronate and zoledronate within their licensed indications for the prevention of fragility fractures.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Search strategies will be used to identify relevant trials (as specified under the inclusion criteria below) and systematic reviews/meta-analyses (for the identification of additional trials). The following databases will be searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid)
- Embase (Ovid)
- Cochrane Database of Systematic Reviews (Wiley Interscience)
- Database of Abstract of Reviews of Effects (Wiley Interscience)
- Cochrane Central Register of Controlled Trials (Wiley Interscience)
- Health Technology Assessment Database (Wiley Interscience)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO)
- Science Citation Index Expanded (Web of Science)
- Conference Proceedings Citation Index - Science (Web of Science)
- BIOSIS (Web of Science)

Current research registers (e.g., ClinicalTrials.gov, WHO International Clinical Trials Registry Platform) will also be searched for on-going and recently completed research projects. Citation searches of key included studies will also be undertaken using the Web of Science database.

Searches will not be restricted by language or publication type. Existing evidence reviews,[15] commissioned by NICE, which included literature published up to June 2008, will be assumed to have identified all papers relevant to this review published prior to 2008. Therefore searches will be limited by date from 2008 until present. The MEDLINE search strategy is presented in Appendix 2. High precision search filters designed to retrieve clinical trials and systematic reviews will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases. Industry submissions and relevant systematic reviews will also be hand-searched in order to identify any further

relevant clinical trials. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

5.2 Inclusion and exclusion criteria

5.2.1 Inclusion criteria

Inclusion criteria have been defined in line with the final scope provided by NICE and are outlined below.

5.2.1.1 Populations

(1) All women aged 65 years and over and men aged 75 years and over.

(2) Women aged 64 years and under and men aged 74 years and under in the presence of risk factors, for example: previous fragility fracture; current use or frequent recent use of oral or systemic glucocorticoids; history of falls; family history of hip fracture; other causes of secondary osteoporosis; low body mass index (BMI) (less than 18.5 kg/m^2); smoking, alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

(3) Women aged 64 years and under and men aged 74 years and under with low BMD (a T-score of -1 standard deviations (SD) or more below the young adult mean).

5.2.1.2 Interventions

Four interventions will be considered within this assessment: alendronate; ibandronate; risedronate and zoledronate.

5.2.1.3 Comparators

Interventions may be compared with each other. Interventions will also be compared with placebo or other non-active treatments (i.e., treatment without the potential to augment bone). Studies which administered calcium and / or vitamin D to patients in both the intervention and comparator arms will be included (e.g. bisphosphonate plus calcium *vs.* placebo plus calcium).

If studies comparing etidronate with one of the four bisphosphonate listed under 5.2.1.2 are identified, these studies and any studies comparing etidronate to placebo will be included in the review and used to inform the evidence network for the Bayesian meta-analysis.

5.2.1.4 Outcomes

The outcome measures to be considered include:

- fragility fracture

  - hip fracture
  - vertebral fracture (where data allow clinical/symptomatic fractures will be reported separately from morphometric/radiographic fractures. Radiographic /morphometric fractures will be defined as those resulting in a 20% or greater reduction in vertebral height)
  - all non-vertebral fracture
  - wrist fracture
  - proximal humerus fracture
  - fragility fracture at other sites
- bone mineral density at the femoral neck assessed by dual energy X-ray absorptiometry (DXA).
- mortality
  - all cause
  - mortality following hip fracture
  - mortality following vertebral fracture
  - mortality following fracture at site other than hip or vertebral
- adverse effects of treatment including but not limited to
  - upper gastrointestinal symptoms
  - osteonecrosis of the jaw
  - hypocalcaemia
  - bone pain
  - atypical femoral fractures
  - influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors
  - conjunctivitis
  - atrial fibrillation
  - stroke
- continuance and concordance (compliance)
- health-related quality of life

- healthcare resource use e.g., hospitalisation, entry into long-term residential care

5.2.1.5 Study design

Randomised controlled trials (RCTs) will be included in the clinical effectiveness systematic review. If no RCTs are identified for an intervention, non-randomised studies may be considered for inclusion. Non-randomised studies may also be included, where necessary, as a source of additional evidence (e.g., relating to adverse events, long-term incidence of fragility fracture, etc.) associated with the interventions.

5.2.2 Exclusion criteria

The following types of studies will be excluded:

- Studies in patients with normal or unspecified BMD who have not been selected based on the presence of risk factors
- Studies in patients with other indications for bisphosphonate treatment e.g. Paget's disease, hypercalaemia of malignancy, metastatic breast cancer
- Studies where interventions are administered not in accordance with licensed indications
- Studies where interventions are co-administered with any other therapy with the potential to augment bone, unless concomitant treatments are specified in the summary of product characteristics
- Systematic reviews and clinical guidelines (these may be used as sources of references)
- Studies which are considered methodologically unsound in terms of study design or the method used to assess outcomes
- Studies which are only published in languages other than English
- Studies based on animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as abstracts or conference presentations only, where insufficient details are reported to allow an assessment of study quality or results.

5.2.3 Study selection

Retrieved studies will be selected for inclusion according to the inclusion and exclusion criteria specified in Sections 5.2.1 and 5.2.2. Studies will be assessed for relevance first by title/abstract, and then finally by full text, excluding at each step studies which do not satisfy the inclusion criteria. One reviewer will examine titles and abstracts for inclusion, and a

second reviewer will check at least 10% of citations. A kappa coefficient will be calculated to measure inter-rater reliability. Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion and exclusion criteria.

5.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form. A draft data extraction form is presented in Appendix 2. Data will be extracted with no blinding to authors or journal. Where multiple publications of the same study are identified, data will be extracted and reported as a single study. A second reviewer will check at least 10% of data extraction forms. Discrepancies will be resolved by discussion. The Assessment Group's approach to handling data obtained from the manufacturers' submissions is detailed in Section 7.

Given the existence of previous NICE commissioned evidence reviews[15] in this area, if the number of new and previously reviewed studies identified for inclusion exceeds 30 we will restrict our data extraction to the new studies published since 2008 and will use the existing data reported in previous reviews[15] for studies published prior to 2008.

5.4 Quality assessment strategy

Methodological quality of RCTs identified for inclusion will be assessed using the Cochrane Collaboration risk of bias assessment criteria. This tool addresses specific domains, namely: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data and selective outcome reporting.

5.5. Methods of analysis/synthesis

Characteristics of included studies including population characteristics, intervention details, comparator details and outcomes will be tabulated and reported in a narrative synthesis.

For outcome measures about which there is interest in simultaneously comparing all treatments, a Bayesian random (treatment) effects network meta-analysis (NMA) will be undertaken, where data allow, using WinBUGS Version 1.4.3 (or OpenBUGS Version 3.2.3). Estimates and 95% credible intervals (CrIs) of the effects of bisphosphonates relative to the reference treatment (i.e. placebo) will be presented as will estimates and 95% CrIs for all pairwise comparisons. Evidence required to inform parameters in the economic model will be generated by taking draws from the posterior distribution i.e. CODA (Convergence Diagnostic and Output Analysis). This will preserve the true underlying joint distribution and

correlation structure of the treatment effects. The analysis and reporting will follow the principles outlined in Ades at al. (2013).[16]

For other outcome measures of interest, Classical pairwise meta-analyses will be performed, where data allow, using Cochrane RevMan Version 5.2 or Stata Version 13.

5.6 Methods for estimating quality of life

Health-related quality of life (HRQoL) data reported by studies included in the clinical effectiveness systematic review will be extracted. In the absence of such evidence, the mathematical model may use evidence on HRQoL drawn from alternative sources.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

There exists a large number of published studies examining the cost-effectiveness of interventions to prevent fragility fracture. A recent systematic review by Müller *et al*.[17] identified 24 studies published between 2006 and 2011 and two earlier reviews by Zethraeus *et al.*[18;19] identified 22 studies in the timeframe 1980-2001 and a further 22 studies published between 2002-2005. The estimates of cost-effectiveness from older published studies are unlikely to be directly applicable to the decision problem outlined in the scope due to the availability of generic bisphosphonates which has reduced the price of bisphosphonates over recent years. For example, alendronate at a dose of 10mg per day costs £301 per annum when using the once-daily branded product, but can be acquired for £10.92 per annum if choosing the weekly non-proprietary preparation. This comparison is based on current list prices[7] but a price of £301 per annum was also applied in the analysis published by Stevenson et al in 2005[20] which was conducted to inform TA160 and TA161. Therefore the TAR group will limit its searches for published economic evaluations to those published in 2006 or later.

A comprehensive search will be undertaken to systematically identify cost-effectiveness literature published in 2006 or later relating to alendronate, ibandronate, risedronate and zoledronate within their licensed indications for preventing fragility fractures in adults who are eligible for fracture risk assessment according to the recommendations in NICE clinical guideline 146.

The search strategy will comprise the following main elements:

- Searching of electronic databases

- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The following databases will be searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid)
- Embase (Ovid)
- Cumulative Index to Nursing and Allied Health Literature (EBSCO)
- Science Citation Index (ISI Web of Knowledge)
- Database of Abstract of Reviews of Effects (Wiley Interscience)
- Health Technology Assessment Database (Wiley Interscience)
- NHS Economic Evaluation Database
- EconLit (Ovid)
- BIOSIS (Web of Knowledge)

Citation searches of key included studies will also be undertaken using the Web of Science database.

Searches will not be restricted by language or publication type. Searches will be limited by date from the start of 2006 until present. The MEDLINE search strategy is presented in Appendix 9.1. High precision search filters designed to identify existing economic evaluations of bisphosphonates to prevent fragility fracture will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases as necessary. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

Additional searches, for example to inform the decision-analytic model, where required in the course of the project, will be undertaken through consultation between the team.

Any existing health economic analyses identified by the searches will be critically appraised using the checklist published by Philips *et al.*[21] In addition, any economic analyses presented in the sponsor submissions to NICE will also be critically appraised using this checklist. Existing cost-effectiveness analyses may also be used to identify sources of evidence to inform structural assumptions and parameter values for the Assessment Group model.

6.2 Development of a *de novo* economic model

A *de novo* economic evaluation will be undertaken from the perspective of the UK NHS and Personal Social Services (PSS). The model will draw together evidence concerning treatment efficacy, continuance and compliance, treatment-related adverse events, resource use and HRQoL. Costs on drug acquisition, administration, hospitalisation, admission to long-term care, adverse events, primary care, and social care will be identified through literature searches and national formularies. In line with current recommendations, costs and health outcomes will be discounted at 3.5%. The primary health economic outcome of the model will be expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. The cost-effectiveness of all interventions and comparators will be compared incrementally against each other.

Sensitivity analysis will be undertaken to examine the key determinants of cost-effectiveness. Probabilistic sensitivity analysis (PSA) will be undertaken to generate information on the likelihood that each treatment produces the greatest amount of net benefit. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

The model will be used to identify treatment thresholds for each intervention. In order to identify treatment thresholds, a cost-effectiveness threshold will need to be assumed. A threshold of £20,000 per QALY will be used in the base case with an alternative threshold of £30,000 per QALY explored in a scenario analysis. All costs related to risk factors assessment including the use of DXA to assess BMD in patients close to a treatment threshold will be excluded from our analysis as these are already recommended by clinical guideline 146.

The thresholds for cost-effective treatment will be expressed using absolute fracture risk, as defined by either FRAX or QFracture, as these tools are recommended by clinical guideline 146 for the assessment of fracture risk. Previous work by the NICE Decision Support Unit[22] suggests that there are limitations to generating an algorithm to robustly predict the cost-effectiveness of interventions based only on absolute fracture risk (defined by either FRAX or QFracture). This is because there are many different ways to achieve a single level of risk using different combinations of patient characteristics (e.g. age, gender, BMD, risk factors) and the cost-effectiveness of treatment is expected to vary according to the exact combination of characteristics. Depending on the availability of epidemiological data, the TAR team may need to employ pragmatic approaches and simplifying assumptions to estimate the average cost-effectiveness of treating individuals at a particular level of absolute risk.

7. Handling the company submission(s)

Data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 12 December 2014. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on economic model submission, will be assessed for clinical validity, reasonableness of assumptions, and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8. Competing interests of authors

None

9. Appendices

Appendix 9.1: Search strategy in Medline

1. exp osteoporosis/
2. osteoporo$.tw.
3. bone diseases, metabolic/
4. exp Bone Density/
5. (bone adj3 densit$).tw.
6. exp fractures, bone/
7. fractures, cartilage/
8. fracture$.ti,ab.
9. bone$ adj2 fragil$.tw.
10. bone mineral densit$.tw.
11. bone loss.tw.
12. bmd.tw.
13. or/1-12

14. (alendron$ or fosomax or fosavance).mp.
15. 121268-17-5.rn.
16. (ibandron$ or boniva or bondronat or bonviva or adronil).mp.
17. 114084-78-5.rn.
18. (risedron$ or actonel or atelvia or benet).mp.
19. 105462-24-6.rn.
20. (zoledron$ or zometa or zomera or aclasta or reclast).mp.
21. 118072-93-8.rn.
22. or/14-21
23. 13 and 22

RCT filter for Medline (Ovid)

1. Randomized controlled trials as Topic/
2. Randomized controlled trial/
3. Random allocation/
4. randomized controlled trial.pt.
5. Double blind method/
6. Single blind method/
7. Clinical trial/
8. exp Clinical Trials as Topic/
9. controlled clinical trial.pt.
10. clinical trial$.pt.
11. multicenter study.pt.
12. or/1-11
13. (clinic$ adj25 trial$).ti,ab.
14. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
15. Placebos/
16. Placebo$.tw.
17. (allocated adj2 random).tw.
18. or/13-17
19. 12 or 18
20. Case report.tw.
21. Letter/
22. Historical article/
23. 20 or 21 or 22

24. exp Animals/
25. Humans/
26. 24 not (24 and 25)
27. 23 or 26
28. 19 not 27

Systematic review filter for Medline (Ovid)

1. meta-analysis as topic/
2. (meta analy$ or metaanaly$).tw.
3. Meta-Analysis/
4. (systematic adj (review$1 or overview$1)).tw.
5. "Review Literature as Topic"/
6. or/1-5
7. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
8. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
9. ((selection adj criteria) or (data adj extraction)).ab.
10. "review"/
11. 9 and 10
12. comment/ or editorial/ or letter/
13. Animals/
14. Humans/
15. 13 not (13 and 14)
16. 12 or 15
17. 6 or 7 or 8 or 11
18. 17 not 16

Economic search filter for Medline (Ovid)

1. exp "costs and cost analysis"/
2. economics/
3. exp economics, hospital/
4. exp economics, medical/
5. economics, nursing/
6. exp models, economic/

7. economics, pharmaceutical/
8. exp "fees and charges"/
9. exp budgets/
10. budget$.tw
11. ec.fs
12. cost$.ti
13. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab
14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti
15. (price$ or pricing$).tw
16. (financial or finance or finances or financed).tw
17. (fee or fees).tw
18. (value adj2 (money or monetary)).tw
19. quality-adjusted life years/
20. (qaly or qalys).af.
21. (quality adjusted life year or quality adjusted life years).af.
22. or/1-21

Appendix 9.2. Draft data extraction form

Draft Data Extraction Form (Version 1.1)	
Trial Details	
Author, year	
Country of corresponding author	
Trial name/number	
RCT design (e.g. multicentre, Phase I, Phase II)	
Geographical Setting (number of study sites, geographical location details)	
Publication type (i.e. full report or abstract)	
Sources of funding	
Inclusion/exclusion criteria	
Primary outcome/secondary outcomes	
No. recruited	
No. randomised	
Date of study	
Interventions	
Intervention name	
Intervention class, dosing regimen and route of administration	

Comparator name	
Comparator dosing regimen and route of administration	
Treatment setting	
Duration of treatment	
Length of follow-up (if different)	
Outcome assessment	
Radiographic assessment of femoral neck BMD (model and manufacturer of DXA machine)	
Fracture assessment, e.g., clinical/radiological assessment, time assessed	
Adverse event reporting	
Continuance and concordance reporting	
Quality of life instrument	
NHS and PSS resource use reporting	
Population Characteristics	
Numbers randomised to treatment groups	
Age	
Gender	
Ethnicity	
Height and weight	
Extent of disease severity at baseline, e.g., osteoporosis, osteopenia, or normal BMD	
Number of years post menopause (women)	
Comorbidities at baseline	
Details of any previous fractures	
Any details of previous conventional treatments (including type, dose and duration)	
Proportion receiving other treatments at baseline	
Details of any other medication at baseline and whether discontinued	
Concomitant medications during study	
History of: previous fragility fracture, glucoglucocorticoid use, falls, family history of hip fracture, low BMI, smoking and alcohol use, secondary osteoporosis	
Any other relevant information	
Were intervention and control groups comparable?	
Analysis	
Statistical techniques used	

Intention to treat description and methods for handling missing data	
Power calculation	
Methodological quality assessment	
Method of random sequence generation	
Method of allocation concealment	
Blinding of participants and caregivers	
Blinding of outcome assessment	
Attrition	
Selective reporting	
Outcomes	
Numbers completing	
Reasons for withdrawal	
Results	
BMD at the femoral neck	
Fracture rates	
Adverse events	
Continuance and concordance	
Health-related quality of life	
Mortality	
Rates of hospitalisation due to fracture	
Rates of new admission to long-term residential care	
Other information	
Summary	
Authors' overall conclusions	
Reviewers' comments	

Appendix 9.3. Timetable/milestones

Milestone	**Date**
Draft protocol	22 August 2014
Final protocol	05 September 2014
Progress report	19th December 2014
Draft assessment report	27 February 2015
Final Assessment report	27 March 2015

10. References

(1) World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of World Health Organization study group. WHO Technical Report Series 843. 1994.

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(9) Summary of Product Characteristics for Zoledronic acid SUN 5 mg solution for infusion. Electronic Medicines Compendium http://www.medicines.org.uk/emc/medicine/28527 [accessed2014 Sept. 2]

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(12) NICE. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. TA161. 2008.

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Appendix 2: Literature Search Strategies

Search strategy in Medline for the clinical effectiveness review

1. exp osteoporosis/
2. osteoporo$.tw.
3. bone diseases, metabolic/
4. exp Bone Density/
5. (bone adj3 densit$).tw.
6. exp fractures, bone/
7. fractures, cartilage/
8. fracture$.ti,ab.
9. (bone$ adj2 fragil$).tw.
10. bone mineral densit$.tw.
11. bone loss.tw.
12. bmd.tw.
13. or/1-12
14. (alendron$ or fosomax or fosavance).mp.
15. 121268-17-5.rn.
16. (ibandron$ or boniva or bondronat or bonviva or adronil).mp.
17. 114084-78-5.rn.
18. (risedron$ or actonel or atelvia or benet).mp.
19. 105462-24-6.rn.
20. (zoledron$ or zometa or zomera or aclasta or reclast).mp.
21. 118072-93-8.rn.
22. or/14-21
23. 13 and 22
24. Randomized controlled trials as Topic/
25. Randomized controlled trial/
26. Random allocation/
27. randomized controlled trial.pt.
28. Double blind method/
29. Single blind method/
30. Clinical trial/
31. exp Clinical Trials as Topic/
32. controlled clinical trial.pt.

33. clinical trial$.pt.
34. multicenter study.pt.
35. or/24-34
36. (clinic$ adj25 trial$).ti,ab.
37. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
38. Placebos/
39. Placebo$.tw.
40. (allocated adj2 random).tw.
41. or/36-40
42. 35 or 41
43. Case report.tw.
44. Letter/
45. Historical article/
46. 43 or 44 or 45
47. exp Animals/
48. Humans/
49. 47 not (47 and 48)
50. 46 or 49
51. 42 not 50
52. 23 and 51
53. limit 52 to yr="2008 -Current"
54. meta-analysis as topic/
55. (meta analy$ or metaanaly$).tw.
56. Meta-Analysis/
57. (systematic adj (review$1 or overview$1)).tw.
58. "Review Literature as Topic"/
59. or/54-58
60. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
61. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
62. ((selection adj criteria) or (data adj extraction)).ab.
63. "review"/
64. 62 and 63
65. comment/ or editorial/ or letter/
66. Animals/

67. Humans/
68. 66 not (66 and 67)
69. 65 or 68
70. 59 or 60 or 61 or 64
71. 70 not 69
72. 23 and 71
73. limit 72 to yr="2008 -Current"

Clinical Trials.gov: US NIH (http://clinicaltrials.gov/)
30th September 2014

67 studies found for: alendronate | received on or after 01/01/2008
2 studies found for: alendronic | received on or after 01/01/2008
no studies found for: fosomax | received on or after 01/01/2008
3 studies found for: fosavance | received on or after 01/01/2008
23 studies found for: ibandronate | received on or after 01/01/2008
20 studies found for: ibandronic | received on or after 01/01/2008
24 studies found for: boniva | received on or after 01/01/2008
23 studies found for: bondronat | received on or after 01/01/2008
24 studies found for: bonviva | received on or after 01/01/2008
no studies found for: adronil | received on or after 01/01/2008
45 studies found for: risedronate | received on or after 01/01/2008
37 studies found for: risedronic | received on or after 01/01/2008
45 studies found for: actonel | received on or after 01/01/2008
45 studies found for: atelvia | received on or after 01/01/2008
13 studies found for: benet | received on or after 01/01/2008
110 studies found for: zoledronate | received on or after 01/01/2008
107 studies found for: zoledronic | received on or after 01/01/2008
110 studies found for: zometa | received on or after 01/01/2008
1 study found for: zomera | received on or after 01/01/2008
110 studies found for: aclasta | received on or after 01/01/2008
110 studies found for: reclast | received on or after 01/01/2008

International Clinical Trials Registry Platform: WHO
(http://apps.who.int/trialsearch/AdvSearch.aspx)
30th September 2014

58 records for 25 trials found for alendronate or alendronic or fosomax or fosavance received on or after 01/01/2008
6 records for 5 trials found for ibandronate or ibandronic received on or after 01/01/2008
4 records for 2 trials found for boniva or bondronat or bonviva or adronil received on or after 01/01/2008

63 records for 35 trials found for risedronate or risedronic or actonel or atelvia or benet received on or after 01/01/2008
118 records for 81 trials found for zoledronate or zoledronic or zometa or zomera or aclasta or reclast received on or after 01/01/2008

Supplementary search strategy for adverse events

1. (alendron$ or fosomax or fosavance).mp.
2. 121268-17-5.rn.
3. (ibandron$ or boniva or bondronat or bonviva or adronil).mp.
4. 114084-78-5.rn.
5. (risedron$ or actonel or atelvia or benet).mp.
6. 105462-24-6.rn.
7. (zoledron$ or zometa or zomera or aclasta or reclast).mp.
8. 118072-93-8.rn.
9. or/1-8
10. (ae or to or po or co).fs.
11. (safe or safety).ti,ab.
12. side effect$.ti,ab.
13. ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
14. (toxicity or complication$ or noxious or tolerability).ti,ab.
15. or/10-14
16. 9 and 15
17. MEDLINE.tw.
18. systematic review.tw.
19. meta analysis.pt.
20. or/17-19
21. 16 and 20

Supplementary search strategy for compliance and concordance search

1. (alendron$ or fosomax or fosavance).mp.
2. 121268-17-5.rn.
3. (ibandron$ or boniva or bondronat or bonviva or adronil).mp.
4. 114084-78-5.rn.
5. (risedron$ or actonel or atelvia or benet).mp.
6. 105462-24-6.rn.
7. (zoledron$ or zometa or zomera or aclasta or reclast).mp.
8. 118072-93-8.rn.
9. or/1-8
10. exp Patient Compliance/
11. (complian$ or comply or adhere$ or capacitance or persistan$ or concordan$).ti,ab.
12. (noncomplian$ or nonadhere$ or nonpersistan$ or nonconcordan$).ti,ab.
13. or/10-12
14. 9 and 13
15. MEDLINE.tw.
16. systematic review.tw.
17. meta analysis.pt.
18. or/15-17
19. 14 and 18

Search strategy in Medline for the cost effectiveness review

1. exp osteoporosis/
2. osteoporo$.tw.
3. bone diseases, metabolic/
4. exp Bone Density/
5. (bone adj3 densit$).tw.
6. exp fractures, bone/
7. fractures, cartilage/
8. fracture$.ti,ab.
9. (bone$ adj2 fragil$).tw.
10. bone mineral densit$.tw.
11. bone loss.tw.
12. bmd.tw.

13. or/1-12
14. (alendron$ or fosomax or fosavance).mp.
15. 121268-17-5.rn.
16. (ibandron$ or boniva or bondronat or bonviva or adronil).mp.
17. 114084-78-5.rn.
18. (risedron$ or actonel or atelvia or benet).mp.
19. 105462-24-6.rn.
20. (zoledron$ or zometa or zomera or aclasta or reclast).mp.
21. 118072-93-8.rn.
22. or/14-21
23. 13 and 22
24. exp "Costs and Cost Analysis"/
25. Economics/
26. exp Economics, Hospital/
27. exp Economics, Medical/
28. Economics, Nursing/
29. exp models, economic/
30. Economics, Pharmaceutical/
31. exp "Fees and Charges"/
32. exp Budgets/
33. budget$.tw.
34. ec.fs.
35. cost$.ti.
36. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
37. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
38. (price$ or pricing$).tw.
39. (financial or finance or finances or financed).tw.
40. (fee or fees).tw.
41. (value adj2 (money or monetary)).tw.
42. quality-adjusted life years/
43. (qaly or qalys).af.
44. (quality adjusted life year or quality adjusted life years).af.
45. or/24-44
46. 23 and 45
47. limit 46 to yr="2006 -Current"

Search strategy in Medline for quality of life

The strategy was adapted from Appendix 4 (page 153) by Stevenson *et al.* (2005) '*A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal' osteoporosis'*.

1. exp osteoporosis/
2. bone diseases, metabolic/
3. osteoporo$.tw.
4. or/1-3
5. (bone adj6 densit$).tw.
6. bone density/
7. bmd.ti,ab.
8. (bone or bones).mp.
9. exp densitometry/
10. tomography, x-ray computed/
11. densit$.tw.
12. 10 and 11
13. 9 or 12
14. 8 and 13
15. 5 or 6 or 7 or 14
16. exp fractures, bone/
17. fractures, cartilage/
18. fracture$.ti,ab.
19. or/16-18
20. 15 or 19
21. 4 and 20
22. (euroqol or euro qol or eq5d or eq 5d).mp.
23. 21 and 22
24. limit 23 to yr="2006 -Current"

Appendix 3: Table of excluded studies – clinical effectiveness review

First author	Reason for exclusion
Adachi *et al.*, 2010[259]	Parallel publication no additional information
Adachi *et al.*, 2010[260]	Parallel publication no additional information
Adachi *et al.*, 2010[261]	Parallel publication no additional information

Adachi *et al.*, 2011[262]	Parallel publication no additional information
Adami *et al.*, 2004[263]	Not treatment of interest - not currently licenced dose
Bauer *et al.*, 2010[264]	Parallel publication no additional information
Bauer *et al.*, 2014[265]	Parallel publication no additional information
Black *et al.*, 2000[266]	Parallel publication no additional information
Black *et al.*, 2003[267]	Not comparator of interest
Black *et al.*, 2005[268]	Not comparator of interest
Black *et al.*, 2006[269]	Extension study, participants not in original randomised groups
Black *et al.*, 2006[270]	Parallel publication no additional information
Black *et al.*, 2010[271]	Parallel publication no additional information
Black *et al.*, 2012[272]	Extension study, participants not in original randomised groups
Black *et al.*, 2009[273]	Parallel publication no additional information
Black *et al.*, 2010[274]	Parallel publication no additional information
Black *et al.*, 2010[275]	Parallel publication no additional information
Black *et al.*, 2011[276]	Parallel publication no additional information
Bone *et al.*, 1997[277]	Not treatment of interest - not currently licenced dose
Boonen *et al.*, 2009[278]	Parallel publication no additional information
Boonen *et al.*, 2010[279]	Parallel publication no additional information
Boonen *et al.*, 2010[280]	Parallel publication no additional information
Boonen *et al.*, 2010[281]	Parallel publication no additional information
Boonen *et al.*, 2011[282]	Parallel publication no additional information
Boonen *et al.*, 2011[283]	Parallel publication no additional information
Boonen *et al.*, 2012[284]	Parallel publication no additional information
Boonen *et al.*, 2012[285]	Parallel publication no additional information
Boonen *et al.*, 2012[286]	Parallel publication no additional information
Colon-Emeric *et al.*, 2010[287]	Parallel publication no additional information
Cosman *et al.*, 2012[288]	Parallel publication no additional information
Delmas *et al.*, 2004[289]	Parallel publication no additional information
Devogelaer *et al.*, 1996[290]	No outcomes of interest
Durchschlag *et al.*, 2006[291]	No outcomes of interest
Eastell *et al.*, 2009[292]	Not outcomes of interest
Eastell *et al.*, 2012[293]	Parallel publication no additional information

Emkey *et al.*, 2009[294]	Parallel publication no additional information
Felsenberg *et al.*, 1999[295]	Not treatment of interest - not currently licenced dose
Felsenberg *et al.*, 2005[295]	Parallel publication no additional information
Genant *et al.*, 2010[296]	Parallel publication no additional information
Grey *et al.*, 2009[297]	Population outside scope of appraisal not licenced indication
Grey *et al.*, 2012[298]	Population outside scope of appraisal not licenced indication
Grey *et al.*, 2014[299]	Population outside scope of appraisal not licenced indication
Guo-Ping *et al.*, 2005[300]	Not comparator of interest
Hakala *et al.*, 2012[301]	Population outside scope of appraisal not licenced indication
Haworth *et al.*, 2010[302]	Population outside scope of appraisal not licenced indication
Haworth *et al.*, 2011[303]	Population outside scope of appraisal not licenced indication
Hochberg *et al.*, 2005[304]	Parallel publication no additional information
Hosking *et al.*, 1998[305]	Not treatment of interest - not currently licenced dose
Hosking *et al.*, 1998[305]	Not treatment of interest - not currently licenced dose
Hwang *et al.*, 2011[306]	Parallel publication no additional information
Hwang *et al.*, 2010[307]	Population outside scope of appraisal not licenced indication
Kasayama *et al.*, 2005[308]	Not treatment of interest - not currently licenced dose
Klotz *et al.*, 2011[309]	Parallel publication no additional information
Langenegger, Opazo & Garcia, 2011[310]	Population outside scope of appraisal not licenced indication
Lindsay *et al.*, 1999[311]	Not treatment of interest – combination therapy with HRT
Lindsay *et al.*, 1999[311]	Not treatment of interest - not currently licenced dose
Majimi *et al.*, 2006[312]	Not treatment of interest - not currently licenced dose
McClung *et al.*, 1998[312]	Not comparator of interest
McClung *et al.*, 2004[313]	Not treatment of interest - not currently licenced dose
McClung *et al.*, 2004[314]	No outcomes of interest
McClung *et al.*, 2005[315]	Not treatment of interest - not currently licenced dose
Mellström *et al.*, 2004[316]	Extension study, participants not in original randomised groups
Miller at al., 2004[317]	Population outside scope of appraisal not licenced indication
Mok *et al.*, 2008[318]	Population outside scope of appraisal not licenced indication
Mortensen *et al.*, 1998[21]	Population outside scope of appraisal not licenced indication
Mortensen *et al.*, 1998[21]	Population outside scope of appraisal not licenced indication
Nakamura *et al.*, 2013[319]	Not treatment of interest - not currently licenced dose

Orwoll *et al.*, 2010[320]	Population outside scope of appraisal not licenced indication
Orwoll *et al.*, 2010[321]	Population outside scope of appraisal not licenced indication
Ravn *et al.*, 1999[322]	Not treatment of interest - not currently licenced dose
Reid *et al.*, 2009[323]	Parallel publication no additional information
Reid *et al.*, 2013[324]	Parallel publication no additional information
Rossini *et al.*, 1994[325]	Not treatment of interest - not currently licenced dose
Roux *et al.*, 2012[326]	Not outcomes of interest
Sambrook *et al.*, 2004[327]	Not comparator of interest
Sambrook *et al.*, 2011[328]	Parallel publication no additional information
Schwartz *et al.*, 2010[329]	Parallel publication no additional information
Seeman *et al.*, 1999[99]	Parallel publication no additional information
Seeman *et al.*, 2009[330]	Parallel publication no additional information
Siris *et al.*, 2008[331]	Parallel publication no additional information
Stakkestad *et al.*, 2003[332]	Not treatment of interest - not currently licenced dose
Tee *et al.*, 2012[333]	Population outside scope of appraisal not licenced indication
Thiébaud *et al.*, 1997[334]	Not treatment of interest - not currently licenced dose
Uchida *et al.*, 2005[335]	Not treatment of interest - not currently licenced dose
Washnich *et al.*, 2004[336]	Not treatment of interest - not currently licenced dose
Westin *et al.*, 2013[337]	Not treatment of interest - not currently licenced dose
Yildrim *et al.*, 2005[338]	No outcomes of interest

Appendix 4: Summary of review findings of compliance and concordance with bisphosphonates

Author and year	Sources searched and dates; types of studies	Measures of compliance and persistence	Bisphosphonates covered	Adherence results	Persistence results
Cramner 2007[135]	MEDLINE for citations of relevant articles accessible between January 1998 and May 2006 Studies were required to contain information of medication-taking practices relating to bisphosphonates and to contain at least one measure of persistence or compliance	Compliance (defined as the extent to which a patient acts in accordance with the prescribed interval and dose as well as dosing regimen) was measured as the medication possession ratio (MPR). This is the number of days' supply received over the length of the follow up. Persistence (defined as the accumulation of time from initiation to discontinuation of therapy) was measured as the number of days of possession without a gap in refills, and the percentage of patients.	Alendronate, risedronate 14 reports	Compliance, ranged from 0.59 to 0.81. When comparing compliance with weekly and daily bisphosphonates, the mean Medication Possession Ratio (MPR) was consistently higher for weekly versus daily therapy (0.58 to 0.76 versus 0.46 to 0.64 for patients receiving weekly and daily bisphosphonate therapy respectively).	The percentage of patients persisting with therapy for 1 year ranged from 17.9% to 78.0%. Persistence was also improved in patients receiving weekly bisphosphonates, assessed by both length of persistence (194 to 269 days [weekly] and 134 to 208 days [daily]) and percentage of persistent patients at the end of the follow-up period (35.7% to 69.7% [weekly] and 26.1% to 55.7% [daily]).
Imaz 2010[136]	Database of Abstracts of Reviews of Effects (DARE); the Health Technology Assessment Database, the International Science Index web of knowledge, Cochrane, Embase and Medline between May 1, 2006 and March 22, 2009.	Two meta-analyses were performed to obtain the mean of persistence days and the mean MPR, after 1 year of follow-up.	Mainly Alendronate and risedronate. Two studies included ibandronate and two studies HRT 15 studies	The pooled MPR mean was 66.9% (95% CI 63.3 to 70.5; five studies) at one year follow-up.	The pooled persistence mean was 184.1 days (95% CI 163.9 to 204.3; five studies) at one year follow-up.
Kothawala 2007[137]	PubMed and Cochrane databases of English- language articles	Persistence - how long a patient receives	Twenty-four studies including 14 in	Pooled adherence rates decreased from	The pooled database-derived persistence rate was 52%

Author and year	Sources searched and dates; types of studies	Measures of compliance and persistence	Bisphosphonates covered	Adherence results	Persistence results
	published from January 1, 1990, to February 15, 2006.	therapy after initiating treatment; compliance how correctly, in terms of dose and frequency, a patient takes the available medication; and adherence t- a measure that assesses both persistence and compliance.11,12	bisphosphonates only, but not reported what type.	53% (95% CI, 52%-54%) for treatment lasting 1 to 6 months to 43% for treatment lasting 7 to 12 months (95% CI, 38%-49%) or 13 to 24 months (43%; 95% CI, 32%-54%). The pooled refill compliance estimate was 68% (95% CI, 63%-72%) for treatment lasting 7 to 12 months and 68% (95% CI, 67%-69%) for treatment lasting 13 to 24 months. The pooled self-reported compliance rate was 62% (95% CI, 48%-75%) for treatment lasting 1 to 6 months and 66% (95% CI, 45%-81%) for treatment lasting 7 to 12 months.	(95% confidence interval [CI], 44%-59%) for treatment lasting 1 to 6 months, 50% (95% CI, 37%-63%) for treatment lasting 7 to 12 months, 42% (95% CI, 20%-68%) for treatment lasting 13 to 24 months, returning to 52% (95% CI, 45%-58%) for treatment lasting more than 24 months. Pooled
Lee 2011[138]	MEDLINE, EMBASE, Biosis and Derwent Drug File for publications (January 1979 to January 2009)	Since adherence was difficult to accurately quantify, preference, compliance and persistence were evaluated.	Alendronate, risedronate 10 studies	Patients' preference and adherence at 12 months were higher with weekly over daily bisphosphonates (≥84% preference for weekly, medication possession ratios	Persistence 12 months 43.6–69.7% weekly vs. 31.7–55.7% daily

Author and year	Sources searched and dates; types of studies	Measures of compliance and persistence	Bisphosphonates covered	Adherence results	Persistence results
				(MPR) 60–76% vs. 46–64%; MPR reported for oral bisphosphonates were 68–71% at 12 months. At 2 years, only 43% of patients had MPR ≥80% for daily and weekly bisphosphonates	
Lloyd-Jones 2006[124]	(Medline, Embase, Cinahl, Biosis, Cochrane Central Register of Controlled Trials, Science Citation Index, Social Sciences Citation Index) to April 2006		Alendronate, risedronate Seventeen relevant studies were identified.	The most relevant evidence for persistence with oral bisphosphonate therapy comes from the UK PEM studies of alendronate and risedronate. 2920 of the 11,916 patients prescribed alendronate by general practitioners (24.5%) appeared to have discontinued therapy within a year. The two most common reasons for stopping treatment were dyspeptic conditions (756, 6.3% of the total cohort) and noncompliance (365, 3.0% of the total cohort). 8,245 of 11,742 patients (70.3%) whose	Evidence from one study in 812 women prescribed alendronate and followed for a mean of ten months, 20.8% had discontinued at two months, and 46.1% by ten months.

Author and year	Sources searched and dates; types of studies	Measures of compliance and persistence	Bisphosphonates covered	Adherence results	Persistence results
				treatment status was recorded were still being prescribed risedronate after 6 months	
Mikyas 2014[139] Review of studies in men	PubMed, MEDLINE, EMBASE, and Cochrane databases were searched 1 January 1998 to 30 June 2012	Adherence included related terms, such as persistence and compliance;	Alendronate and other treatments 18 studies in men	The percentage of males adherent to bisphosphonates [medication possession ratio (MPR)>0.8] over a 1-year period ranged from 32 % to 64 %	
Vieira 2014[140]	Systematic review of articles on BPs adherence for treatment of osteoporosis, indexed on MEDLINE (via PubMed) databases, from inception of databases until January 2013	27studies met the eligibility criteria. Identified studies covered a wide range of aspects regarding adherence and associated factors, adherence and fracture, adherence and BPs dosage. The studies were mostly observational. Data not pooled	Alendronate, risedronate, ibandronate, zoledronate	<u>Studies in treatments of interest:</u> Cohort study 775 taking zoledronate; 275 taking ibandronate; the proportion of patients with high adherence for the zoledronate and the 2 ibandronate cohorts was 62.8% versus 36.0% and 33.3%. But approximately 30% of patients taking zoledronate did not receive a second infusion. Cohort study 22,363 new users of an oral BP (alendronate, risedronate, ibandronate): Patients receiving oral BPs on a monthly basis showed higher rates of medication compliance. Overall compliance 43% Cohort study 451,113 new patients: alendronate, etidronate, risedronate: Persistence with therapy declined from 63% at 1 year to 46% at 2 years and 12% at 9 years. RCT 341 postmenopausal women taking -weekly alendronate or monthly ibandronate: MPR ranged from 93% to 100%.	

Author and year	Sources searched and dates; types of studies	Measures of compliance and persistence	Bisphosphonates covered	Adherence results	Persistence results
				Retrospective observational: 2,990 women taking-weekly (alendronate or risedronate) or monthly ibandronate: Patients treated with a monthly regimen were 37% less likely to be non-persistent and were more compliant, with a 5% higher absolute MPR, than women treated with weekly regimens. Cohort study 32,804 patients taking weekly risedronate or weekly alendronate(brand or generic): Patients initiated on weekly oral generic alendronate showed a statistically significant lower persistence to BP therapy compared to patients initiated on weekly oral branded risedronate and weekly oral branded alendronate	

Appendix 5: Adverse events reported across included RCTs

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
Alendronate vs. placebo						
Black 1996 [57] (FIT I)	*Any AE:* PBO, 819/1005 (81.5%) ALN10mg/d, 724/1022 (70.8%) *Withdrawals due to AE:* PBO, 96/1005 (9.6%) ALN10mg/d, 78/1022 (7.6%) *Hospitalisation:* PBO, 300/1005 (29.9%) ALN10mg/d, 250/1022 (24.5%) *Death:* PBO, 21/1005 (2.1%) ALN10mg/d, 24/1022 (2.3%)	*Any UGI:* PBO, 402/1005 (40%) ALN10mg/d, 422/1022 (41.3%) *Dyspepsia:* PBO, 158/1005 (15.7%) ALN10mg/d, 155/1022 (15.2%) *Abdominal pain:* PBO, 98/1005 (9.8%) ALN10mg/d, 121/1022 (11.8%) *Nausea:* PBO, 97/1005 (9.7%) ALN10mg/d, 96/1022 (9.4%) *Oesophagitis:* PBO, 4/1005(0.4% ALN10mg/d, 7/1022 (0.7%) *Oesophageal ulcer:* PBO, 2/1005 (0.2%) ALN10mg/d, 3/1022 (0.3%) *Duodenal ulcer,* PBO, 6/1005 (0.6%) ALN10mg/d, 2/1022				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		(0.2%) *Acid regurgitation:* PBO, 71/1005 (7.1%) ALN10mg/d, 71/1022 (6.9%) *Gastritis:* PBO, 20/1005 (2%) ALN10mg/d, 24/1022 (2.3%) *Gastric ulcer:* PBO, 16/1005 (1.6%) ALN10mg/d, 7/1022 (0.7%) *Other oesophageal:* PBO, 11/1005 (1.2%) ALN10mg/d, 16/1022 (1.6%) *Other gastric:* PBO, 2/1005 (0.2%) ALN10mg/d, 4/1022 (0.4%)				
Cummings 1998 [66] (FIT II)	*Death:* PBO, 40/2218 (1.8%) ALN10mg/d, 37/2214 (1. 7%) *Hospitalisation:* PBO, 596/2218 (26.9%) ALN10mg/d, 644/2214 (29.1%) *Withdrawals due to*	*Any UGI:* PBO, 1047/2218 (47.2) ALN10mg/d, 1052/ 2214 (47.5%) *Abdominal pain:* PBO, 325/2218(14.7%) ALN10mg/d, 322/2057 (14.5%)				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	AE: PBO, 227/2218 ALN10mg/d, 221/2214	*Oesophagitis:* PBO, 10/2218 (0.5%) ALN10mg/d, 19/2214 (0.9%) *Oesophageal ulcer:* PBO, 4/2218 (0.2%) ALN10mg/d, 4/2214 (0.2%) *Acid regurgitation:* PBO, 194/2218 (8.7%) ALN10mg/d, 204/ 2214 (9.2%) *Other oesophageal:* PBO, 41/2218 (1.8%) ALN10mg/d, 44/2214 (2%)				
Greenspan 2003 [70]	*Hospitalisations:* PBO, 26/93 (28%) ALN10mg/d, 34/93 (37%)	*Dysphagia:* PBO, 2/93 (2.0%) ALN10mg/d, 3/93 (3.0%) *Oesophagitis:* PBO, 21/93 (23%) ALN10mg/d, 26/93 (28%) *Indigestion,* PBO, 4/93 (4%) ALN10mg/d, 6/93 (6%) *Heartburn:* PBO, 15/93 (16%) ALN10mg/d, 17/93				*Myocardial infarction:* PBO, 1/93 (1.0%) ALN10mg/d, 2/93 (2.0%) *HBP:* PBO, 3/93 (3.0%) ALN10mg/d, 5/93 (5.0%) *Deep venous thrombosis:* PBO, 0/93 (0%) ALN10mg/d, 1/93 (1%) *Menstrual spotting:*

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		(18%)				PBO, 9/93 (10%) ALN10mg/d, 7/93 (8%) *Menstrual Cramps:* PBO, 0/93 (0%) ALN10mg/d, 0/93 (0%) *Endometrial biopsy:* PBO, 1/93 (1%) ALN10mg/d, 2/93 (2%) *Peripheral oedema:* PBO, 12/93 (13%) ALN10mg/d, 9/93 (10%) *Weight gain:* PBO, 8/93 (9%) ALN10mg/d, 6/93 (6%) *Chest pain:* PBO, 13/93 (14%) ALN10mg/d, 16/93 (17%) *Endometrial biopsy:* PBO, 1/93 (1%) ALN10mg/d, 2/93 (2%) *Breast tenderness:* PBO, 16/93 (17%) ALN10mg/d, 22/93 (24%) *Falls:* PBO, 42/93 (45%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						ALN10mg/d, 52/93 (56%)
Greenspan 2002 [69]	*Any AE:* PBO, 153/164 (35.0%) ALN10mg/d, 152/163 (33.0%)	*Any UGI:* PBO, 57/164 (35%) ALN10mg/d, 54/163 (33%) Any serious UGI: PBO, 3/164 (1.9%) ALN10mg/d, 1/163 (0.6%)				
Liberman 1995 [78].	*Withdrawals due to AE:* PBO, 24/397 (6%) ALN10mg/d, 8/196 (4.1%)	*Discont due to UGI:* PBO, 8/397 (2.0%) ALN10mg/d, 2/196 (1.0%) *Abdominal pain:* PBO, 19/397 (4.8%) ALN10mg/d, 13/196 (6.6%) *Nausea:* PBO, 16/397 (4%) ALN10mg/d, 7/196 (3.6%) *Dyspepsia:* PBO, 14/397 (3.5%) ALN10mg/d, 7/196 (3.6%)				*Musculoskeletal pain:* PBO, 10/397 (2.5%) ALN10mg/d, 8/196 (4.1%) *Constipation:* PBO, 7/397 (1.8%) ALN10mg/d, 7/196 (3.1%) *Diarrohea:* PBO, 12/397 (3.1%) ALN10mg/d, 4/196 (1.8%)
Orwoll 2000 [85]	*Serious AE:* PBO, 22/95 (23%) ALN10mg/d, 27/146 (18%) *Withdrawals due to AE:*	*Any UGI:* PBO, 21/95 (22%) ALN10mg/d, 37/146 (25%) *Abdominal pain:* PBO, 4/95 (4%)				*Nervous system:* PBO, 19/95 (20%) ALN10mg/d, 37/146 (25%) *Skin:* PBO, 21/95 (22%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	PBO, 10/95 (11.0%) ALN10mg/d, 4/146 (3.0%)	ALN10mg/d, 12/146 (8%) *Dyspepsia:* PBO, 1/95 (1%) ALN10mg/d, 9/146 (6%) *Acid regurgitation:* PBO, 5/95 (5%) ALN10mg/d, 7/146 (5%) *Oesophagitis:* PBO, 1/95 (1%) ALN10mg/d, 1/146 (1%)				ALN10mg/d, 33/146 (23%) *Urogenital:* PBO, 16/95 (17%) ALN10mg/d, 25/146 (17%) *Respiratory:* PBO, 47/95 (49%) ALN10mg/d, 66/146 (45%) *Musculoskeletal:* PBO, 50/95 (53%) ALN10mg/d, 68/146 (47%) *Cardiovascular:* PBO, 16/95 (17%) ALN10mg/d, 23/146 (16%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
Pols 1999 [86] (FOSIT) .	*Any AE:* PBO, 643/958 (67.1%) ALN10mg/d, 662/950 (69.7%) *Serious AE:* PBO, 63/958 (6.5%) ALN10mg/d, 60/950 (6.3%) *Withdrawals due to AE:* PBO, 61/958 (6.4%) ALN10mg/d, 53/950 (5.6%)	*Any UGI:* PBO, 185/958 (19.3%) ALN10mg/d, 202/950 (21.3%) *Dyspepsia:* PBO, 2/958 (0.2%) ALN10mg/d, 24/950 (2.5%) *Abdominal pain:* PBO, 81/958 (8.5%) ALN10mg/d, 95/950 (10%) *Nausea:* PBO, 37/958 (3.9%) ALN10mg/d, 44/950 (4.6%) *Acid regurgitation:* PBO, 24/958, (2.5%) ALN10mg/d, 22/950, (2.3%) *Gastritis:* PBO, 20/958 (2.1%) ALN10mg/d, 26/950 (2.8%) *Gastric ulcer:* PBO, 1/958 (0.1%) ALN10mg/d, 4/950 (0.4%) *Reflux oesophagitis:* PBO, 3/958 (0.3%) ALN10mg/d, 4/950 (0.4%) *Oesophagitis:* PBO, 3/958 (0.3%) ALN10mg/d, 4/950 (0.4%) *Duodenal ulcer:*				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
Saag 1998 [93]	*Any AE:* PBO, 126/159 (79%) ALN10mg/d, 662/950 (69.7%) *Serious AE:* PBO, 34/159 (21%) ALN10mg/d, 60/950 (6.3%) *Withdrawals due to AE:* PBO, 8/159 (5%) ALN10mg/d, 53/950 (5.6%)	*Any UGI:* PBO, 26/159 (16%) ALN10mg/d, 40/157 (25%) *Serious UGI:* PBO, 2/159 (1%) ALN10mg/d, 2/157 (1%) *Oesophageal irritation:* PBO, 4/159 (3%) ALN10mg/d, 3/157 (2%) *Abdominal pain:* PBO, 8/159 (5%) ALN10mg/d, 15/157 (10%) *Peptic ulcer:* PBO, 2/159 (1%) ALN10mg/d, 2/157 (1%)				*Musculoskeletal pain:* PBO, 25/159 (16%) ALN10mg/d, 25/157 (16%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
Bone 2000 [59]	*Any AE:* PBO, 45/50 (90% ALN10mg/d, 80/92 (87%) *Serious AE:* PBO, 5/50 (10%) ALN10mg/d, 13/92 (14%) *Withdrawals due to AE:* PBO, 5/50 (10%) ALN10mg/d, 6/92 (6%)	*Any UGI:* PBO, 11/50 (22%) ALN10mg/d, 25/92 (27%) *Dyspepsia:* PBO, 3/50 (6%) ALN10mg/d, 7/92 (8%) *Abdominal pain:* PBO, 2/50 (4%) ALN10mg/d, 7/92 (8%) *Peptic ulcer:* PBO, 0/50 (0%) ALN10mg/d, 0/92 (0%) *Oesophagitis:* PBO, 2/50 (4%) ALN10mg/d, 5/92 (5%)				
Ibandronate vs. placebo						
McClung 2009 [82] USA.	*Any AE:* PBO, 64/83 (77.1%) IBN150mg/m, 60/77 (77.9%) *Serious AE:* PBO, 1/83 (1.2%) IBN150mg/m, 3/77 (3.9%) *Withdrawals due to AE:* PBO, 3/83 (3.6%) IBN150mg/m, 7/77	*Any UGI:* PBO, 20/83 (24.1%) IBN150mg/m, 24/77 (31.2%) *Dyspepsia:* PBO, 4/83 (4.8%) IBN150mg/m, 4/77 (5.2%) *Reflux oesophagitis:* PBO, 3/83 (3.6%) IBN150mg/m, 4/77 (5.2%)	*Flu-like symptoms* PBO, 0/83 (0%) IBN150mg/m, 4/83 (5.2%)			*Arthralgia:* PBO, 8/83 (9.6%) IBN150mg/m, 12/77 (15.6%) *Myalgia:* PBO, 2/83 (2.4%) IBN150mg/m, 5/77 (6.5%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	(9.1%)	*Nausea:* PBO, 3/83 (3.6%) IBN150mg/m, 5/77 (6.5%)				
Chesnut *et al.*, 2004 [114] (BONE)	*Any AE:* PBO, 867/975 (88.9%) IBN2.5mg/d, 879/977 (90%) *Serious AE:* PBO, 211/975 (21.6%) IBN2.5mg/d, 234/977 (24%) *Withdrawals due to AE:* PBO, 183/975 (18.9%) IBN2.5mg/d, 181/977 (18.5%) *Deaths:* PBO, 10/975 (1%) IBN2.5mg/d, 11/977 (1.1%)	*Duodenal ulcer:* PBO, 9/975 (0.9%) IBN2.5mg/d, 1/977 (0.1%) *Dyspepsia:* PBO, 89/975 (9.1%) IBN2.5mg/d, 111/977 (11.4%) *Belching:* PBO, 2/975 (0.2%) IBN2.5mg/d, 4/977 (0.4%) *Gastritis:* PBO, 21/975 (2.2%) IBN2.5mg/d, 22/977 (2.3%) *Gastroenteritis:* PBO, 54/975 (5.5%) IBN2.5mg/d, 54/977 (5.5%) *GI pain:* PBO, 25/975 (2.6%) IBN2.5mg/d, 19/977 (1.9%) *Nausea:* PBO, 61/975 (6.3%) IBN2.5mg/d, 41/977 (4.2%) *Oesophageal ulcer:*				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		PBO, 1/975 (0.1%) IBN2.5mg/d, 2/977 (0.2%) *Oesophageal stenosis:* PBO, 1/975 (0.1%) IBN2.5mg/d, 0/977 (0%) *Oesophagitis:* PBO, 10/975 (1%) IBN2.5mg/d, 15/977 (1.5%) *Stomach ulcer:* PBO, 6/975 (0.6%) IBN2.5mg/d, 3/977 (0.3%) *Vomiting:* PBO, 24/975 (2.5%) IBN2.5mg/d, 29/977 (3%)				
Risedronate vs. placebo						
McClung 2001[80] (HIPS)	*Any AE:* PBO, 2805/3134 (89.5%) RIS5mg/d, 2786/3104 (89.8%) *Serious AE:* PBO, 973/3134 (31%) RIS5mg/d, 943/3104 (30.3%) *Withdrawals due to AE:* PBO, 564/3134 (18.0%)	*Any UGI:* PBO, 684/3134 (21.8%) RIS5mg/d, 657/3104 (21.2%) *Moderate to severe:* PBO, 258/3134 (8.3%) RIS5mg/d, 279/3104 (9%) *Abdominal pain:* PBO, 288/3134 (9.2%)				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	RIS5mg/d, 550/3104 (17.7%)	RIS5mg/d, 250/3104 (8.1%) *Dyspepsia:* PBO, 254/3134 (8.1%) RIS5mg/d, 255/3104 (8.2%) *Oesophagitis:* PBO, 59/3134 (1.9%) RIS5mg/d, 54/3104 (1.7%) *Oesophageal ulcer:* PBO, 14/3134 (0.4%) RIS5mg/d, 9/3104 (0.3%)				
Fogelman 2000 [68] (BMD-MN)	*Any AE:* PBO, 172/180 (95.6%) RIS5mg/d, 169/177 (95.5%) *Serious AE:* PBO, 27/180 (15%) RIS5mg/d, 26/177 (15%) *Withdrawals due to AE:* PBO, 14/180 (8.0%) RIS5mg/d, 19/177 (11.0%)	*Any UGI:* PBO, 47/180 (26.0%) RIS5mg/d, 40/177 (23.0%) *Abdominal pain:* PBO, 22/180 (12%) RIS5mg/d, 23/177 (13%) *Dyspepsia:* PBO, 18/180 (10.0%) RIS5mg/d, 15/177 (8%) *Oesophagitis:* PBO, 4/180, (2%) RIS5mg/d, 3/177, (2%) *Gastritis:*				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		PBO, 0/180 (0%) RIS5mg/d, 3/177 (2%) *Oesophageal ulcer:* PBO, 1/180 (1%) RIS5mg/d, 3/177 (2%) *Stomach ulcer:* PBO, 5/180 (3%) RIS5mg/d, 1/177 (1%)				
Harris 1999 [72] (VERT-NA)	*Any AE:* PBO, 774/815 (95.0%) RIS5mg/d, 785/813 (97.0%) *Serious AE:* PBO, 219/815 (27%) RIS5mg/d, 237/813 (29%) *Withdrawals due to AE:* PBO, 136/815 (17.0%) RIS5mg/d, 138/812 (17.0%)	*Any UGI:* PBO, 219/815 (27.0%) RIS5mg/d, 245/813 (30.0%) *Moderate-to-severe UGI:* PBO, 102/815 (13%) RIS5mg/d, 106/813 (13%) *Dyspepsia:* PBO, 92/815 (11.0%) RIS5mg/d, 105/813 (12.9%) *Abdominal pain:* PBO, 97/815 (12%) RIS5mg/d, 103/813 (13%) *Gastritis:* PBO, 23/815 (3%) RIS5mg/d, 31/813				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		(4%) *Oesophagitis:* PBO, 13/815, (2%) RIS5mg/d, 11/813, (1%) *Duodenitis* PBO, 2/815 (0.2%) RIS5mg/d, 9/813 (1%)				
Sorensen 2003 [102] (VERT-NA extension)	*Serious AE:* PBO, 39/130 (30%) RIS5mg/d, 33/135 (24.4%) *Withdrawals due to AE:* PBO, 16/130 (12.3%) RIS5mg/d, 10/135 (7.4%)	*Any UGI:* PBO, 18/130 (13.8%) RIS5mg/d, 17/135 (12.2%) *Dyspepsia:* PBO, 4/130 (3.1%) RIS5mg/d, 9/135 (6.7%) *Abdominal pain:* PBO, 7/130 (5.4%) RIS5mg/d, 7/135 (5.2%) *Oesophagitis:* PBO, 1/130 (0.8%) RIS5mg/d, 2/135 (1.5%) *Oesophageal ulcer:* PBO, 1/130 (0.8%) RIS5mg/d, 1/135 (0.7%) *Gastritis:* PBO, 3/130 (2.3%) RIS5mg/d, 1/135 (0.7%)				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		Gastric ulcer: PBO, 1/130 (0.8%) RIS5mg/d, 0/135 (0%)				
Hooper 2005 [74] (VERT-MN)	*Any AE:* PBO, 115/125 (92.0%) RIS5mg/d, 122/129 (95.0%) *Serious AE:* PBO, 22/125 (18%) RIS5mg/d, 12/129 (9%) *Withdrawals due to AE:* PBO, 8/125 (6.0%) RIS5mg/d, 7/129 (5.0%)	*Any UGI:* PBO, 20/125 (16.0%) RIS5mg/d, 25/129 (19.0%) *Dyspepsia:* PBO, 12/125 (9.6%) RIS5mg/d, 8/129 (6.2%) *Abdominal pain:* PBO, 6/125 (4.8%) RIS5mg/d, 9/129 (7%) *Oesophagitis:* PBO, 4/125 (3.2%) RIS5mg/d, 4/129 (3.1%) *GI disorder:* PBO, 2/125 (1.6%) RIS5mg/d, 4/129 (3.1%)				
		Gastritis: PBO, 3/125 (2.4%) RIS5mg/d, 2/129 (1.6%) *Oesophageal ulcer:* PBO, 2/125 (1.6%) RIS5mg/d, 1/129 (0.8%)				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		Stomach ulcer: PBO, 1/125 (0.8%) RIS5mg/d, 0/129 (0%) *Duodenal ulcer:* PBO, 0/125 (0%) RIS5mg/d, 1/129 (0.8%)				
Reginster 2000 [87] (VERT-MN)	*Any AE:* PBO, 370/407 (91.0%) RIS5mg/d, 374/407 (92.0%) *Serious AE:* PBO, 135/407 (33%) RIS5mg/d, 151/407 (37%) *Withdrawals due to AE:* PBO, 81/407 (20%) RIS5mg/d, 63/407 (15%)	*Any UGI:* PBO, 104/407 (26.0%) RIS5mg/d, 109/407 (27.0%) *Abdominal pain:* PBO, 32/407 (8%) RIS5mg/d, 50/407 (12%) *Dyspepsia:* PBO, 44/407 (11.0%) RIS5mg/d, 36/407 (9.0%) *Oesophagitis:* PBO, 11/407, (3%) RIS5mg/d, 10/407, (2%) *Gastritis:* PBO, 14/407 (3%) RIS5mg/d, 9/407 (2%) *Stomach ulcer:* PBO, 2/407 (0.5%) RIS5mg/d, 6/407				*Cancer:* PBO, 17/407 (4.2%) RIS5mg/d, 19/407 (4.7%) *Cardiovascular:* PBO, 38/407 (9.3%) RIS5mg/d, 38/407 (9.3%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		(1%) *Duodenitis:* PBO, 0/407 (0%) RIS5mg/d, 2/407 (0.5%) *Oesophageal ulcer:* PBO, 3/407 (1%) RIS5mg/d, 2/407 (0.5%) *Duodenal ulcer:* PBO, 1/407 (0.5%) RIS5mg/d, 2/407 (0.5%)				
Boonen 2009 [60]	*Any AE:* PBO, 68/93 (73%) RIS35mg/w, 134/191 (70%) *Serious AE:* PBO, 15/93 (16%) RIS35mg/w, 29/191 (15%) *Withdrawals due to AE:* PBO, 9/93 (9.7%) RIS35mg/w, 7/191 (3.7%) *Death:* PBO, 3/93 (3%) RIS35mg/w, 2/191 (1%)	*Any UGI:* PBO, 17/93 (18%) RIS35mg/w, 16/191 (8%) *Moderate to severe UGI:* PBO, 4/93 (4%) RIS35mg/w, 6/191 (3%) *Constipation:* PBO, 5/93 (5%) RIS35mg/w, 16/191 (8%)	*Influenza:* PBO, 5/93 (5%) RIS35mg/w, 11/191 (6%)			*Arthralgia:* PBO, 8/93 (9%) RIS35mg/w, 11/191 (6%) *Back pain:* PBO, 2/93 (2%) RIS35mg/w, 13/191 (7%) *Nasopharyngitis:* PBO, 5/93 (5%) RIS35mg/w, 11/191 (6%) *Headache:* PBO, 0/93 (0%) RIS35mg/w, 10/191 (5%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
Zoledronate vs. placebo						
Black 2007 [58] (HORIZON-PFT)	*Any AE:* PBO, 3616/3852 (93.9%) ZOL5mg/y, 3688/3862 (95.5%) *Serious AE:* PBO, 1158/3852 (30.1%) ZOL5mg/y, 1126/3862 (29.2%) *Withdrawals due to AE:* PBO, 70/3852 (1.8%) ZOL5mg/y, 80/3862 (2.1%) *Death:* PBO, 112/3852 (2.9%) ZOL5mg/y, 130/3862 (3.4%)		*Flu-like symptoms:* PBO, 61/3852 (1.6%) ZOL5mg/y, 301/3862 (7.8%)	*Osteonecrosis of the jaw:* Reports that no cases of osteonecrosis of the jaw were observed	*Atrial fib:* PBO, 73/3852 (1.9%) ZOL5mg/y, 94/3862 (2.4%) *Serious:* PBO, 20/3852 (0.5%) ZOL5mg/y, 50/3862 (1.3%)	*Pyrexia:* PBO, 79 /3852 (2.1%) ZOL5mg/y, 621//3862 (16.1%) *Headache:* PBO, 90/3852 (2.3%) ZOL5mg/y, 273/3862 (7.1%) *Arthralgia:* PBO, 76/3852 (2.0%) ZOL5mg/y, 245/3862 (6.3%) *Myalgia:* PBO, 66/3852 (1.7%) ZOL5mg/y, 365/3862 (9.5%) *Myocardial infarction:* PBO, 45/3852 (1.2%) ZOL5mg/y, 38/3862 (1.0%)
Reid *et al.*, 2010 [104] (HORIZON-PFT) Adverse events in first three days following administration		*Any UGI:* PBO, 80/3852 (2.1%) ZOL5mg/y, 300/3862 (7.8%) *Abdominal pain:* PBO, 17/3852 (0.4%) ZOL5mg/y, 40/3862 (1.0%) *Anorexia:* PBO, 7/3852 (0.2%)	*Flu-like symptoms:* PBO, 49/3852 (1.3%) ZOL5mg/y, 303/3862 (7.8%) *Fever:* PBO, 70/3852 (1.8%) ZOL5mg/y, 663/3862 (17.2%) *Chills:* PBO, 23/3852 (0.6%)			*Eye inflammation:* PBO, 2/3852 (0.1%) ZOL5mg/y, 14/3862 (0.4%) *Eye pain:* PBO, 0/3852 (0.0%) ZOL5mg/y, 9/3862 (0.2%) *Dizziness/vertigo:* PBO, 40/3852 (1.0%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
		ZOL5mg/y, 45/3862 (1.2%) *Diarrhoea:* PBO, 23/3852 (0.6%) ZOL5mg/y, 55/3862 (1.4%) *Nausea:* PBO, 37/3852 (1.0%) ZOL5mg/y, 158/3862 (4.1%) *Vomiting:* PBO, 6/3852 (0.2%) ZOL5mg/y, 73/3862 (1.9%)	ZOL5mg/y, 171/3862 (4.4%) *Any – fever, chills, hot flush:* PBO, 96/3852 (2.5%) ZOL5mg/y, 785/3862 (20.3%)			ZOL5mg/y, 75/3862 (1.9%) *Oedema peripheral:* PBO, 4/3852 (0.1%) ZOL5mg/y, 18/3862 (0.5%) *Syncope:* PBO, 0/3852 (0.0%) ZOL5mg/y, 7/3862 (0.2%) *Pain:* PBO, 11/3852 (0.3%) ZOL5mg/y, 74/3862 (1.9%) *Thirst:* PBO, 0/3852 (0.0%) ZOL5mg/y, 11/3862 (0.3%) *Insomnia:* PBO, 1/3852 (0.0%) ZOL5mg/y, 8/3862 (0.2%) *Tremor:* PBO, 2/3852 (0.1%) ZOL5mg/y, 11/3862 (0.3%) *Any body pains:* PBO, 180/3852 (4.7%) ZOL5mg/y, 770/3862 (19.9%) *Joint swelling:* PBO, 0/3852 (0.0%) ZOL5mg/y, 14/3862

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						(0.4%) *Musculoskeletal pain:* PBO, 73/3852 (1.9%) ZOL5mg/y, 190/3862 (4.9%) *Musculoskeletal stiffness:* PBO, 5/3852 (0.1%) ZOL5mg/y, 37/3862 (1.0%) *Diffuse musculoskeletal pain:* PBO, 114/3582 (3.0%) ZOL5mg/y, 606/3862 (15.7%) *Nasopharyngitis:* PBO, 5/3852 (0.1%) ZOL5mg/y, 17/3862 (0.4%) *Headache:* PBO, 59/3852 (1.5%) ZOL5mg/y, 225/3862 (5.8%) *Malaise:* PBO, 16/3852 (0.4%) ZOL5mg/y, 45/3862 (1.2%) *Fatigue:* PBO, 63/3852 (1.6%) ZOL5mg/y, 205/3862 (5.3%)
Lyles 2007 [79]	*Any AE:*		*Flu-like symptoms:*	*Osteonecrosis of the*	*Atrial fib:*	*Serum creatinine*

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
(HORIZON-RFT)	PBO, 852/1057 (80.6%) ZOL5mg/y, 867/1054 (82.3%) *Serious AE:* PBO, 436/1057 (41.2%) ZOL5mg/y, 404/1054 (38.3%) *Withdrawals due to AE:* PBO, 18/1057 (1.7%) ZOL5mg/y, 21/1054 (2.0%) *Death:* PBO, 141/1057 (13.3%) ZOL5mg/y, 101/1054 (9.6%)		PBO, 3/1057 (0.3%) ZOL5mg/y, 6/1054 (0.6%)	*jaw:* Reports that no cases of osteonecrosis of the jaw were observed	PBO, 38/1057 (3.6%) ZOL5mg/y, 46/1054 (4.4%) *Stroke:* PBO, 38/1057 (3.6%) ZOL5mg/y, 46/1054 (4.4%)	*>0.5 mg/dl:* PBO, 50/900 (5.6%) ZOL5mg/y, 55/886 (6.2%) *Creatinine clearance <30 ml/min:* PBO, 65/891 (7.3%) ZOL5mg/y, 72/882 (8.2%) *Arthralgia:* PBO, 23/1057 (2.2%) ZOL5mg/y, 33/1054 (3.1%) *Myalgia:* PBO, 9/1057 (0.9%) ZOL5mg/y, 33/1054 (3.1%) *Pyrexia:* PBO, 9/1057 (0.9%) ZOL5mg/y, 73/1054 (6.9%) *Headache:* PBO, 9/1057 (0.9%) ZOL5mg/y, 16/1054 (1.5%) *Myocardial infarction:* PBO, 17/1057 (1.6%) ZOL5mg/y, 13/1054 (1.2%)
Boonen 2012[61]	*Any AE:* PBO, 466/611 (76.3) ZOL5mg/y, 534/588			*Osteonecrosis of the jaw:* Reports that no cases of osteonecrosis		*Pyrexia:* PBO, 23/611 (3.8%) ZOL5mg/y, 143/588

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	(90.8) *Serious AE:* PBO, 154/611 (25.2) ZOL5mg/y, 149/588 (25.3) *Death:* PBO, 18/611 (2.9) ZOL5mg/y, 15/588 (2.6)			of the jaw were observed		(24.3%) *Myalgia:* PBO, 25/611 (4.1%) ZOL5mg/y, 129/588 (21.9%) *Headache:* PBO, 27/611 (4.4%) ZOL5mg/y, 82/588 (13.9%) *Arthralgia:* PBO, 68/611 (11.1%) ZOL5mg/y, 123/588 (20.9%) *Back pain:* PBO, 74/611 (12.1%) ZOL5mg/y, 84/588 (14.3%) *Myocardial infarction:* PBO, 2/611 (0.3%) ZOL5mg/y, 9/588 (1.5%) *Cardiac failure:* PBO, 4/611 (0.7%) ZOL5mg/y, 1/588 (0.2%) *Hypertension:* PBO, 46/611 (7.5%) ZOL5mg/y, 50/588 (8.5%) *Cardiac disorder:* PBO, 30/611 (4.9%) ZOL5mg/y, 31/588

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						(5.3%) *Angina pectoris:* PBO, 7/611 (1.1%) ZOL5mg/y, 6/588 (1.0%)
McClung 2009 [81]	*Any AE:* PBO, 186/202 (92.1%) ZOL5mg/y, 173/181 (95.6%)	*Nausea:* PBO, 16/202 (7.9%) ZOL5mg/y, 21/181 (11.6%)		*Osteonecrosis of the jaw:* Reports that no cases of osteonecrosis of the jaw were observed		*Urinary tract infection:* PBO, 25/202 (12.4%) ZOL5mg/y, 16/181 (8.8%) *Upper Res inf.* PBO, 23/202 (11.4%) ZOL5mg/y, 19/181 (10.5%) *Pyrexia:* PBO, 9/202 (45%) ZOL5mg/y, 38/181 (21.0%) *Chills:* PBO, 6/202 (3.0%) ZOL5mg/y, 33/181 (18.2%) *Fatigue:* PBO, 8/202 (4.0%) ZOL5mg/y, 18/181 (9.9%) *Headache:* PBO, 23/202 (11.4%), ZOL5mg/y, 37/181 (20.4%) *Nasopharyngitis:* PBO, 23/202 (11.4%) ZOL5mg/y, 17/181

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						(9.4%) *Arthralgia:* PBO, 39/202 (19.3%) ZOL5mg/y, 34/181 (18.8%) *Pain:* PBO, 7/202 (3.5%) ZOL5mg/y, 27/181 (14.9%) *Myalgia:* PBO, 14/202 (6.9%) ZOL5mg/y, 41/181 (22.7%) *Back pain:* PBO, 24/202 (11.9%) ZOL5mg/y, 30/181 (16.6%) *Pain in extremity:* PBO, 20/202 (9.9%) ZOL5mg/y, 29/181 (16.0%)
Head-to-head – Zoledronate vs. risedronate						
Reid 2009[90] (HORIZON)	ZOL5mg/y vs. RIS5mg/d – treatment subgroup: *Any AE:* 211/272 (78%) *vs.* 186/273 (68%) *Serious AE:* 50/272 (18%) *vs.* 54/237 (20%) *Withdrawals due to AE:*	ZOL5mg/y vs. RIS5mg/d – treatment subgroup: *Upper abdominal pain* 16/272 (6%) *vs.* 9/273 (3%) *Abdominal pain* 7/272 (3%) *vs.* 6/273 (2%) *Dyspepsia* 15/272 (6%) *vs.* 13/273 (5%) *Nausea* 30/272 (11%)	*Flu-like symptoms* Treatment subgroup: ZOL5mg/y 15 (6%) RIS5mg/d 3 (1%) Prevention subgroup: ZOL5mg/y 10 (7%) RIS5mg/d 1 (1%)	*Bone pain:* Treatment subgroup: ZOL5mg/y 13 (5%) RIS5mg/d 5 (2%) Prevention subgroup: ZOL5mg/y 0 (0%) RIS5mg/d 4 (3%) *Osteonecrosis of the jaw:* Reports that no	*Atrial fibrillation:* Treatment subgroup: ZOL5mg/y 0 (0%) RIS5mg/d 0 (0%) Prevention subgroup: ZOL5mg/y 3 (2%) RIS5mg/d 0 (0%)	ZOL treatment, RIS treatment, ZOL prevention, RIS prevention: Worsening rheumatoid arthritis 21 (8%) 17 (6%) 5 (3%) 4 (3%) Constipation 5 (2%) 7 (3%) 4 (3%) 3 (2%) Diarrhoea 12 (4%) 10

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	3/272 (1%) *vs.* 3/273 (1%) *Death:* 3/272 (1%) *vs.* 3/273 (1%) ZOL5mg/y vs. RIS5mg/d – prevention subgroup: *Any AE:* 111/144 (77%) *vs.* 93/144 (65%) *Serious AE:* 26/144 (18%) *vs.* 23/144 (16%) *Withdrawals due to AE:* 6/144 (4%) *vs.* 3/144 (2%) *Death:* 1/144 (<1%) *vs.* 0/144 (0%)	*vs.* 21/273 (8%) *Vomiting* 17/272 (6%) *vs.* 7/273 (3%) *Gastritis* 2/272 (1%) *vs.* 4/273 (1%) *Gastro-oesophageal reflux* 3/272 (1%) *vs.* 1/273 (<1%) ZOL5mg/y vs. RIS5mg/d – prevention subgroup: *Upper abdominal pain* 5/141 (3%) *vs.* 4/141 (3%) *Abdominal pain* 3/141 (2%) *vs.* 2/141 (1%) *Dyspepsia* 8/141 (6%) *vs.* 5/141 (3%) *Nausea* 10/141 (7%) *vs.* 14/141 (10%) *Vomiting* 3/141 (2%) *vs.* 3/141 (2%) *Gastritis* 3/141 (2%) *vs.* 2/141 (1%) *Gastro-oesophageal reflux* 2/141 (1%) *vs.* 5/141 (3%)		cases of osteonecrosis of the jaw were observed		(4%) 3 (2%) 0 (0%) Rectal haemorrhage 1 (<1%) 0 (0%) 3 (2%) 0 (0%) Urinary tract infection 16 (6%) 13 (5%) 5 (3%) 4 (3%) Back pain 14 (5%) 17 (6%) 4 (3%) 9 (6%) Hypertension 14 (5%) 11 (4%) 4 (3%) 6 (4%) Asthenia 9 (3%) 6 (2%) 7 (5%) 9 (6%) Anaemia 8 (3%) 10 (4%) 2 (1%) 2 (1%) Vertigo 6 (2%) 3 (1%) 2 (1%) 2 (1%) Fatigue 8 (3%) 4 (1%) 5 (3%) 2 (1%) Oedema peripheral 7 (3%) 6 (2%) 5 (3%) 3 (2%) Weight increase 7 (3%) 8 (3%) 2 (1%) 5 (3%) Pain in limbs 8 (3%) 2 (1%) 5 (3%) 3 (2%) Musculoskeletal chest pain 7 (3%) 0 (0%) 1 (1%) 0 (0%) Dizziness 7 (3%) 2 (1%) 3 (2%) 2 (1%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						Sciatica 7 (3%) 0 (0%) 3 (2%) 1 (1%) Insomnia 7 (3%) 3 (1%) 1 (1%) 3 (2%) Rash 3 (1%) 7 (3%) 0 (0%) 1 (1%) Allergic dermatitis 2 (1%) 6 (2%) 0 (0%) 2 (1%) Palpitations 1 (<1%) 0 (0%) 3 (2%) 3 (2%) Chest pain 1 (<1%) 0 (0%) 1 (1%) 3 (2%) Cataract 3 (1%) 4 (1%) 4 (3%) 3 (2%) Keratoconjunctivitis sicca 0 (0%) 0 3 (2%) 0 (0%) Bronchitis 2 (1%) 1 (<1%) 3 (2%) 5 (3%) Contusion 5 (2%) 1 (<1%) 3 (2%) 1 (1%) Fall 4 (1%) 4 (1%) 3 (2%) 0 (0%) Musculoskeletal stiff ness 1 (<1%) 0 (0%) 4 (3%) 1 (1%) Joint swelling 1 (<1%) 2 (1%) 3 (2%) 0 (0%) Musculoskeletal pain 5 (2%) 2 (1%) 1 (1%) 5 (3%)

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						Anxiety 1 (<1%) 3 (1%) 3 (2%) 2 (1%) Depression 4 (1%) 5 (2%) 3 (2%) 2 (1%) Proteinuria 4 (1%) 0 (0%) 0 3 (2%) Paraesthesia 2 (1%) 1 (<1%) 4 (3%) 1 (1%)
Head-to-head – Alendronate vs. Ibandronate						
Miller 2008[83] (MOTION)	*Any AE:* ALN70mg/w, 659/859 (75.4%) IBN150mg/m, 632/874 (73.6%) *Serious AE:* ALN70mg/w, 39/859 (4.5%) IBN150mg/m, 55/874 (6.4%) *Death:* ALN70mg/w, 2/859 (0.2%) IBN150mg/m, 4/874 (0.5%)	*Dyspepsia:* ALN70mg/w, 48/859 (5.6%) IBN150mg/m, 60/874 (6.9%)	*Influenza:* ALN70mg/w, 36/859 (4.2%) IBN150mg/m, 49/874 (5.6%)			*Nasopharyngitis:* ALN70mg/w, 41/859 (4.8%) IBN150mg/m, 51/874 (5.8%) *Arthralgia:* ALN70mg/w, 49/859 (5.7%) IBN150mg/m, 47/874 (5.5%) *Back pain:* ALN70mg/w, 45/859 (5.2%) IBN150mg/m, 60/874 (6.9%) *Hypertension:* ALN70mg/w, 51/859 (5.9%) IBN150mg/m, 68/874 (7.8%)
Head-to-head – Alendronate vs. Risedronate						
Rosen 2005[92] (FACT)	*Any AE:* ALN70mg/w, 394/515	*Upper GI:* ALN70mg/w,				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
	(76.5%) RIS35mg/w, 399/527 (76.1%) *Serious AE:* ALN70mg/w, 45/515 (8.7%) RIS35mg/w, 41/527 (7.8%) *Withdrawals due to AE:* ALN70mg/w, 33/515 (6.4%) RIS35mg/w, 33/527 (6.2%)	116/515 (22.5%) RIS35mg/w, 106/527 (20.1%) *Causing discontinuation:* ALN70mg/w, 13/515 (2.5%) RIS35mg/w, 16/527, (3.0%)				
Bonnick 2006 [106] (FACT)	*Any AE:* ALN70mg/w, 358/411 (87.1%) RIS35mg/w, 358/414 (86.5%) *Serious AE:* ALN70mg/w, 51/411 (12.4%) RIS35mg/w, 56/414 (13.5%) *Withdrawals due to AE:* ALN70mg/w, 9/411 (2.2%) RIS35mg/w, 9/414 (2.2%)	*Upper GI:* ALN70mg/w, 128/411 (24.8%) RIS35mg/w, 122/414 (22.9%)				
Reid 2006[119]	*Any AE:*	*Any UGI:*				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
(FACTS)	ALN70mg/w, 306/468 (65.4%) RIS35mg/w, 314/468 (67.1%) *Serious AE:* ALN70mg/w, 24/468 (5.1%) RIS35mg/w, 47/468 (10.0%) *Withdrawals due to AE:* ALN70mg/w, 20/468 (4.3%) RIS35mg/w, 28/468 (6%)	ALN70mg/w, 95/468 (20.3%) RIS35mg/w, 94/468 (20.1%); *Serious UGI:* ALN70mg/w, 2/468 (0.4%) RIS35mg/w, 4/468 (0.9%)				
Reid 2008[107] (FACTS) (Extension to Reid 2006[119]) Seventy-two of the original 75 international sites Merck & Co., Inc.	*Any AE:* ALN70mg/w, 301/403 (74.7 %) RIS35mg/w, 299/395 (75.7%) *Serious AE:* ALN70mg/w, 42/403 (10.4%) RIS35mg/w, 44/395 (11.1%) *Withdrawals due to AE:* ALN70mg/w, 5/403 (1.2%) RIS35mg/w, 5/395 (1.3%)	*Any UGI:* ALN70mg/w, 91/403 (22.6%) RIS35mg/w, 73/395 (18.5%) *Serious UGI:* ALN70mg/w, 3/403 (0.7%) RIS35mg/w, 2/395 (0.5%) *Discontinued because of UGI AE:* ALN70mg/w, 1/403 (0.2%) RIS35mg/w, 2/395 (0.5%)				

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
Head-to-head – Alendronate vs. Zoledronate						
Hadji 2012[71] (ROSE)	*Any AE:* ALN70mg/w, 145/194 (74.7%) ZOL5mg/y, 320/408 (78.4%) *Serious AE:* ALN70mg/w, 21/194 (10.8%) ZOL5mg/y, 43/408 (10.5%) *Withdrawals due to AE:* ALN70mg/w, 19/194 (9.8%) ZOL5mg/y, 2/408 (0.5%)	*Any UGI:* ALN70mg/w, 57/194 (29.4%) ZOL5mg/y, 75/408 (18.4%) *Upper abdominal pain:* ALN70mg/w, 13/194 (6.7%) ZOL5mg/y, 12/408 (2.9%) *Dyspepsia:* ALN70mg/w, 14/194 (7.2%) ZOL5mg/y, 3/408 (0.7%) *Nausea:* ALN70mg/w, 11/194 (5.7%) ZOL5mg/y, 23/408 (5.6%)	*Flu-like symptoms:* ALN70mg/w, 5/194 (32.4%) ZOL5mg/y, 132/408 (32.4%)	*Bone pain*: ALN70mg/w, 7/408 (3.6%) ZOL5mg/y, 23/194 (5.6%) *Osteonecrosis of the jaw:* Reports that no cases of osteonecrosis of the jaw were observed		*Chills:* ALN70mg/w, 3/194 (1.5%) ZOL5mg/y, 13/408 (3.2%) *Fatigue:* ALN70mg/w, 4/194 (2.1%) ZOL5mg/y, 24/408 (5.9%) *Pyrexia:* ALN70mg/w, 2/194 (1%) ZOL5mg/y, 21/408 (5.1%) *Arthralgia:* ALN70mg/w, 21/408 (10.8%) ZOL5mg/y, 55/194 (13.5%) *Musculoskeletal and connective tissue:* ALN70mg/w, 64/194 (33.0%) ZOL5mg/y, 186/408 (45.6%) *Back pain:* ALN70mg/w, 20/408 (10.3%) ZOL5mg/y, 53/194 (13.0%) *Osteoarthritis:*

Author details (trial acronym), time point	Any AE, serious AE, withdrawals due to AE, death – n/N (%)	Upper GI AE – n/N (%)	Flu-like symptoms – n/N (%)	Hypocalcaemia, atypical femoral fracture, bone pain, jaw osteonecrosis, conjunctivitis– n/N (%)	Stroke, atrial fibrillation – n/N (%)	Other– n/N (%)
						ALN70mg/w, 9/408 (4.6%) ZOL5mg/y, 15/194 (3.7%) *Pain in extremity:* ALN70mg/w, 5/408 (2.6%) ZOL5mg/y, 30/194 (7.4%)

Appendix 6: Summary of review findings of adverse events associated with bisphosphonates

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
Bobba *et al.* (2006)[120]	MEDLINE 1975 to 2006 14 studies in alendronate, eight studies in risedronate, ten studies in ibandronate and nine studies in zoledronate. RCTs and observational studies were included	Not reported	Alendronate, ibandronate, risedronate, zoledronate	Data not pooled	The authors concluded that the adverse events associated with alendronate, risedronate and oral ibandronate are minimal. However, zoledronate may be compromised by renal toxicity. Myalgias and arthralgias are evident in the acute phase following i.v. administration
Crandall (2001)[121]	MEDLINE 1996 to 2001 9 RCTs and 7 clinical trials	Postmenopausal osteoporosis, Paget's disease, participants with breast cancer and participants taking glucocorticoids	Risedronate	Data not pooled	Across six RCTs of risedronate for any condition, safety data indicated that risedronate is similar to placebo and does not include any notable upper GI adverse event rate.
Kherani, Papaioannou and Adachi (2002)[122]	Not reported Pivotal trials	Postmenopausal osteoporosis	Alendronate, risedronate	RR of discontinuing treatment with alendronate, 1.15 (95%CI 0.93 to 1.42) RR of discontinuing treatment with risedronate, 0.94 (95%CI 0.80 to 1.10)	Both alendronate and risedronate studies demonstrate similar adverse event rates between placebo and active treatment.
Lloyd-Jones 2006[124]	(Medline, Embase, Cinahl, Biosis, Cochrane Central Register of Controlled Trials,	Not reported	Alendronate, risedronate	Data not pooled	UK prescription event monitoring studies suggest that therapy with daily

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
	Science Citation Index, Social Sciences Citation Index) to April 2006 34 studies				alendronate or risedronate is associated with a high level of reporting of a number of conditions in the first month of therapy, particularly those affecting the upper gastrointestinal tract
Umland and Boyce (2001)[123]	MEDLINE 1966 to 2000 Clinical studies and review articles	Osteoporosis and Paget's disease	Risedronate	Data not pooled	Risedronate has been associated with a lower incidence of gastric ulcers than alendronate. However, that adverse events associated with risedronate are generally comparable to those observed with placebo in most clinical trials
Krueger *et al.* (2007)[126]	MEDLINE 1966 to 2007 11 case reports and 26 case series studies	Some studies in osteoporosis, others not reported	Mainly zoledronate	Data not pooled	Intravenous bisphosphonates, especially zoledronate, are more likely to predispose patients to osteonecrosis of the jaw. However, in addition to bisphosphonate use, there appear to be several other factors involved in the development of osteonecrosis of the jaw. Other risk factors noted from the included studies were dental extraction or trauma to the jaw exposing part of the bone
Van den Wyngaert,	MEDLINE 1966 to 2005	Three studies	Zoledronate	Data not pooled	Across the studies, 69.3%

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
Huizing and Vermorken (2006)[127]	22 studies based on retrospective chart reviews without control,	included patients with osteoporosis			of patients had undergone a dental extraction prior to the development of osteonecrosis. This would confirm the importance of trauma in the initiation of the disease.
Woo, Hellstein and Kalmar (2006)[128]	MEDLINE 1966 to 2006 29 case reports	85% of affected patients had multiple myeloma or metastatic breast cancer, and 4% had osteoporosis	Zoledronate, alendronate	Data not pooled	The prevalence of osteonecrosis in patients with cancer is 6% to 10% and the prevalence in those taking alendronate for osteoporosis is unknown. More than half of all cases (60%) occur after dentoalveolar surgery, and the remaining 40% are probably related to infection, denture trauma, or other physical trauma
Lee *et al.* (2014)[129]	MEDLINE, EMBASE to 2012 12 cohort and case-control studies	Non-cancer patients	Oral and i.v. administered bisphosphonates	Use of BPs was associated with a significantly increased risk of ONJ or ON of other sites [odds ratio (OR) 2.32; 95 % CI 1.38–3.91; I2=91 %]. The summary OR was 2.91 (95 % CI 1.62–5.22; I 2=85.9 %) for adjusted studies. Use of BPs was associated with higher risk on ONJ	Bisphosphonates in non-cancer patients is associated with a substantial risk for jaw osteonecrosis and that patients receiving i.v. bisphosphonates are at highest risk

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
				(OR 2.57; 95 % CI 1.37–4.84; I 2=92.2 %) than ON of other sites (OR 1.79; 95 % CI 0.71–4.47; I 2=83.3 %). Meta-regression analysis did not find design characteristics or outcome definitions to be significant sources of heterogeneity	
Giusti, Hamdy and Papapoulos (2010)[130]	PubMed to 2012 27 case series or case reports	Women treated with a bisphosphonate at a dosing regimen used for the prevention or treatment of osteoporosis	In most cases, the bisphosphonate was alendronate,	Data not pooled	The analysis allowed the clinical identification of patients at risk of developing atypical fractures. However, that long-term bisphosphonate therapy is not a prerequisite for development of atypical fractures. Moreover, the use of glucocorticoids and proton pump inhibitors are important risk factors
Gedmintas, Solomon and Kim (2013)[131]	MEDLINE and EMBASE databases 1990 to 2012 Five case-control and six cohort studies	Mainly women	mainly alendronate but also ibandronate, risedronate, zoledronate	Bisphosphonate exposure was associated with an increased risk of subtrochanteric, femoral shaft, and AFF, with adjusted RR of 1.70 (95% confidence interval [CI], 1.22–2.37). studies examining at	There is an increased risk of atypical fracture among bisphosphonate users. However, atypical fractures are rare events even in bisphosphonate users.

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
				least 5 years of bisphosphonate use showed adjusted RR of 1.62 (95% CI, 1.29–2.04).	
Andrici, Tio and Eslick (2012)[132]	MEDLINE, PubMed, EMBASE to 2013 Seven cohort or case-control studies	Any who had filed a prescription for any antiresorptive drug	Any bisphosphonate	odds ratio of 1.74 (95%CI, 1.19 to2.55)	The results suggest a possible association between oral bisphosphonates and oesophageal cancer, which was increased with a longer exposure period. An increased risk was observed for Etidronate, but not Alendronate
Sun *et al.* (2013)[133]	Four cohort studies and three case control studies	Not reported	Alendronate was the main bisphosphonate	Pooled relative risk (RR) 1.23, 95 % CI 0.79–1.92] and case–control studies [pooled odds ratio (OR) 1.24, 95 % CI 0.98–1.57] secondary analysis, no significant increased risk of oesophageal cancer was found in alendronate users (pooled RR 1.08, 95 % CI 0.67–1.75 in cohort studies; pooled OR 1.16, 95 % CI 0.82–1.63 in case– control studies)	Bisphosphonate treatment was not significantly associated with excess risk of oesophageal cancer
Loke, Jeevanantham and	MEDLINE to 2008	Patients with	Alendronate,	Bisphosphonates	Bisphosphonates were

Author and year	Sources searched and dates; types of studies	Types of patients	Bisphosphonates covered	Pooled results	Conclusions
Singh (2009)[134]	Eleven studies including nine RCTs	osteoporosis or fractures	risedronate, zoledronate	significantly increased risk of serious adverse events for atrial fibrillation compared to placebo (OR 1.47, 95% CI 1.01 to 2.14; nine RCTs). One case-control study found that patients with atrial fibrillation were more likely to have used bisphosphonates than control patients (adjusted OR 1.86, 95% CI 1.09 to 3.15, I =46%). The second case-control study found no association	associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents precluded any definitive conclusions with respect to risk

Appendix 7: Network meta-analyses supplementary results data

Summary of the trials included in the network meta-analysis of vertebral fractures. Treatments are coded as; 1= placebo , 2= risedronate , 3= alendronate, 4=zoledronate, 5= ibandronate 150 mg monthly, 6= ibandronate 2.5 mg daily. Assessment method coded as; 0 = morphometric, 1 = clinical.

Study	study duration	assessment	treatments		events		number of participants	
(author, year)	(years)	method	arm 1	arm2	arm 1	arm2	arm 1	arm2
Cohen 1999 [65]	1	0	1	2	5	2	35	34
Fogelman 2000 [68]	2	0	1	2	17	8	125	112
Harris 1999 [72] (VERT-NA) USA	3	0	1	2	93	61	678	696
Reginster 2000 [87] (VERT-MN)	3	0	1	2	89	53	346	344
Hooper 2005 [74]	2	0	1	2	10	10	125	129
Reid 2000 [88]	1	0	1	2	9	3	60	60
Boonen 2009[60]	2	0	1	2	0	1	80	191
Ringe 2006[91]	1	1	1	2	20	8	158	158
Liberman 1995[78]	3	0	1	3	22	5	355	175
Orwoll 2000 [85]	2	0	1	3	7	1	94	146
Black 1996 [57] (FIT I)	3	0	1	3	192	83	965	981
Cummings 1998 [66] (FIT II)	4	0	1	3	78	43	2077	2057
Dursun 2001 [67]	1	0	1	3	14	12	35	38
Carfora 1998 [62]	2.5	0	1	3	4	1	34	34
Boonen 2012[61]	2	0	1	4	28	9	574	533
Black 2007[58] (HORIZON-PFT)	3	1	1	4	84	19	3861	3875
Lyles 2007[79] (HORIZON-RFT)	3	1	1	4	39	21	1062	1065
Chesnut 2004[45] (BONE)	3	0	1	6	93	46	975	977
Muscoso, 2004	1	NA	2	3	0	2	100	1000
HORIZON-SIO Reid, 2009	1	NA	2	4	3	5	381	378
MOTION Miller, 2008	1	1	3	5	5	5	859	874

Summary of the trials included in the network meta-analysis of non-vertebral fractures. Treatments are coded as; 1= placebo , 2= risedronate , 3= alendronate, 4=zoledronate, 5= ibandronate 150 mg monthly, 6= ibandronate 2.5 mg daily.

Study	study duration	treatments		events		number of participants	
(author, year)	(years)	arm 1	arm2	arm 1	arm2	arm 1	arm2
Fogelman 2000 [68]	3	1	2	13	7	125	112
Harris 1999 [72] (VERT-NA) USA	3	1	2	52	33	815	812
Reginster 2000 [87] (VERT-MN)	2	1	2	51	36	406	406
Hooper 2005 [74]	1	1	2	6	5	125	129
Ringe 2006[91]	4	1	2	17	10	158	158
Black 1996 [57] (FIT I)	3	1	3	148	122	1005	1022
Cummings 1998 [66] (FIT II)	4	1	3	294	261	2077	2057
Orwoll 2000 [85]	2	1	3	5	6	94	146
Pols 1999 [86] (FOSIT)	1	1	3	37	19	958	950
Bone 2000[59]	2	1	3	4	5	50	92
Black 2007[58] (HORIZON-PFT)	0.92	1	4	388	292	3861	3875
Lyles 2007[79] (HORIZON-RFT)	3	1	4	107	79	1062	1065
Chesnut 2004[45] (BONE)	3	1	6	80	89	975	977
Miller 2008[83] (MOTION)	1	3	5	12	14	859	874

Summary of the trials included in the network meta-analysis of hip fractures. Treatments are coded as; 1= placebo , 2= risedronate , 3= alendronate, 4=zoledronate, 5= ibandronate 150 mg monthly.

Study	study duration	treatments		events		number of participants	
(author, year)	(years)	arm 1	arm2	arm 1	arm2	arm 1	arm2
McClung 2001[80]	3	1	2	46	32	1821	1812
Harris 1999 [72] (VERT-NA) USA	3	1	2	15	12	815	812
Reginster 2000 [87] (VERT-MN)	3	1	2	11	9	406	406
Black 1996 [57] (FIT I)	3	1	3	22	11	1005	1022
Cummings 1998 [66] (FIT II)	4	1	3	24	19	2218	2214
Greenspan 2002 [69]	2	1	3	4	2	164	163
Black 2007[58] (HORIZON-PFT)	3	1	4	88	52	3861	3875
Lyles 2007[79] (HORIZON-RFT)	3	1	4	33	79	1062	1065
Lester 2008[76] (ARIBON)	2	1	5	0	1	19	21
Muscoso 2004[84]	1	2	3	0	1	100	1000

Summary of the trials included in the network meta-analysis of wrist fractures. Treatments are coded as; 1= placebo , 2= risedronate , 3= alendronate, 4= ibandronate 150 mg monthly.

Study	study duration	treatments		events		number of participants	
(author, year)	(years)	arm 1	arm2	arm 1	arm2	arm 1	arm2
Harris 1999 [72] (VERT-NA) USA	3	1	2	22	14	815	812
Reginster 2000 [87] (VERT-MN)	3	1	2	21	15	406	406
Black 1996 [57] (FIT I)	3	1	3	41	22	1005	1022
Cummings 1998 [66] (FIT II)	4	1	3	70	83	2218	2214
McClung 2009[82]	1	1	4	0	1	83	77
Lester 2008[76] (ARIBON)	2	1	4	1	1	19	21
Muscoso 2004[84]	1	2	3	0	1	100	1000

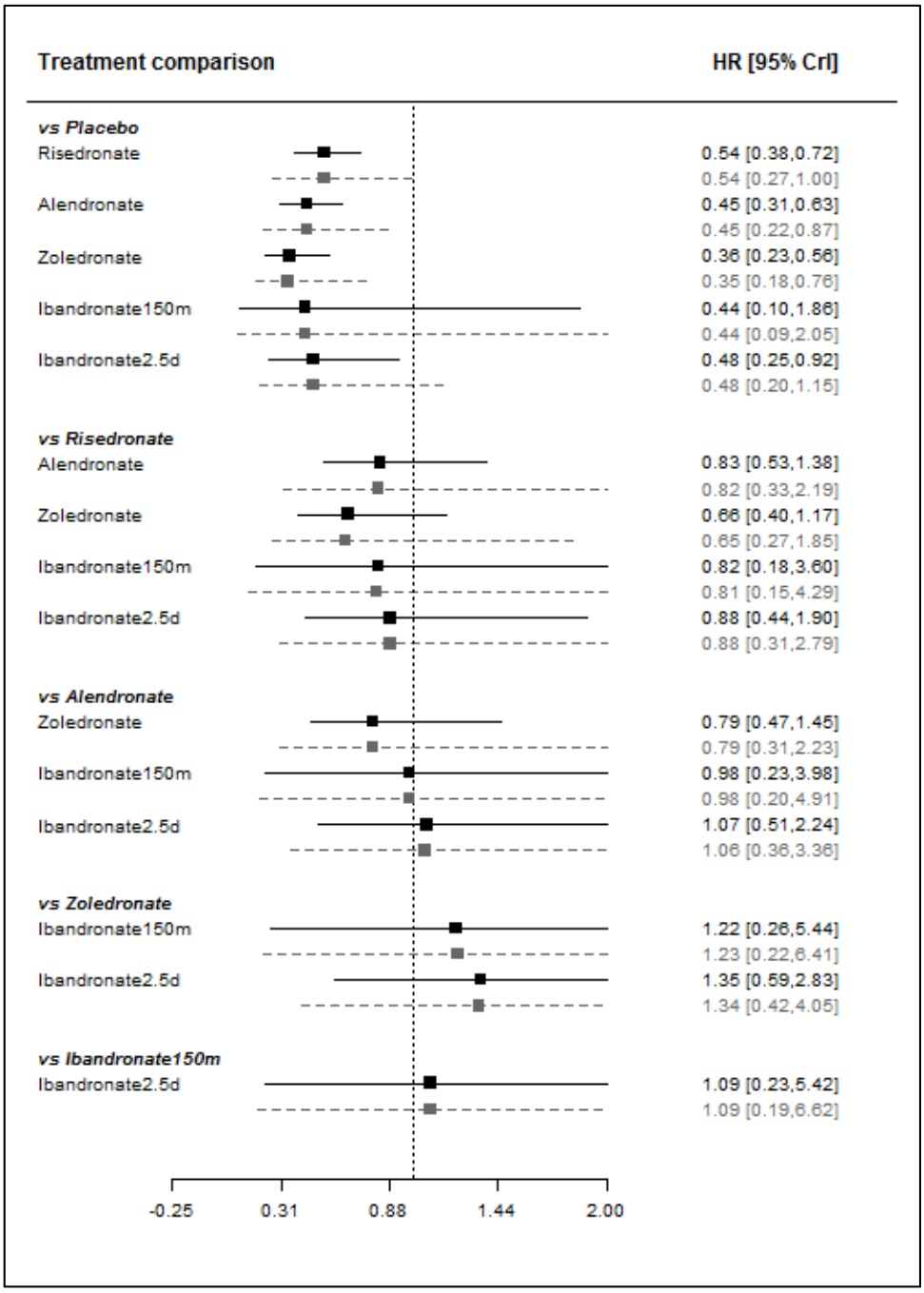
Summary of the trials included in the network meta-analysis of femoral neck BMD. Treatments are coded as; 1= placebo , 2= alendronate , 3= risedronate, 4=zoledronate, 5= ibandronate 150 mg monthly, 6= ibandronate 2.5 mg daily, 7= ibandronate 3mg every 3 months.

Study	study duration	treatments		% change in BMD		SE % change in BMD		number of participants		Mean difference	
(author, year)	(years)	arm 1	arm2	arm 1	arm2	arm 1	arm2	arm 1	arm2	% change in BMD	SE
Adami 1995 [55]	2	1	2	-2.58	1.19	0.89	0.88	62	61	NA	NA
Bone 2000[59]	2	1	2	-0.6	2.9	0.60	0.50	46	87	NA	NA
Dursun 2001 [67]	1	1	2	2.33	3.75	0.73	1.00	35	38	NA	NA
Pols 1999 [86] (FOSIT)	1	1	2	-0.2	2.3	0.15	0.15	884	863	NA	NA
Greenspan 2003 [70]	3	1	2	-0.65	4.2	0.53	0.59	93	93	NA	NA
Orwoll 2000 [85]	2	1	2	-0.1	2.5	0.50	0.40	81	128	NA	NA
Saag 1998 [93]	0.92	1	2	-1.2	1	0.40	0.40	142	145	NA	NA
Klotz 2013[75]	1	1	2	-2.06	1.65	0.78	1.12	53	45	NA	NA
Fogelman 2000 [68]	2	1	3	-1	1.3	0.32	0.44	180	175	NA	NA
Harris 1999 [72] (VERT-NA)	3	1	3	-1.2	1.6	0.45	0.60	417	457	NA	NA
Leung 2005 [77]	1	1	3	1.1	1.8	0.90	0.70	34	31	NA	NA
Cohen 1999 [65]	1	1	3	-2.94	-1.04	0.84	0.94	36	34	NA	NA
Reid 2000 [88]	1	1	3	-0.29	1.63	0.50	0.62	43	52	NA	NA
Boonen 2009[60]	2	1	3	0.73	1.71	0.34	0.25	93	191	NA	NA
Choo 2011[64]	2	1	3	-5.56	-2.55	2.92	2.89	52	52	NA	NA
Taxel 2010[97]	1	1	3	-2	0	0.61	0.61	20	20	NA	NA
McClung 2009 [81]	2	1	4	-1.35	1.64	0.29	0.31	202	181	NA	NA
Boonen 2012[61]	2	1	4	0.1	3.4	0.58	0.60	63	56	NA	NA
McClung 2009[82]	1	1	5	-0.73	1.09	0.46	0.33	83	77	NA	NA

Sarioglu 2006[94]	1	2	3	3.7	2.6	0.96	0.60	25	25	NA	NA
Miller 2008[83] (MOTION)	1	2	5	2.3	2.1	0.07	0.06	822	836	NA	NA
Reid 2009[90] (HORIZON)	1	3	4	0.39	1.4	0.25	0.26	374	373	NA	NA
Miller 2005[47](MOBILE)	1	5	6	2.22	1.71	0.21	0.21	320	318	NA	NA
Delmas 2006 [49] (DIVA)	1	6	7	1.6	2.3	0.21	0.20	381	368	NA	NA
Black 1996 [57] (FIT I)	3	1	2	-0.31	3.54	0.18	0.17	1005	1022	4.10	0.25
Cummings 1998 [66] (FIT II)	4	1	2	-0.8	3.6	0.16	0.16	2218	2214	4.60	0.23
Greenspan 2002 [69]	2	1	2	-0.36	2.84	0.06	0.35	164	163	3.40	0.50
Liberman 1995[78]	3	1	2	-1.28	4.65	0.30	0.47	397	196	5.90	0.50
Hooper 2005 [74]	2	1	3	-2.43	2.29	0.33	0.20	125	125	3.30	0.27
Reginster 2000 [87] (VERT-MN)	3	1	3	-0.97	2.09	0.37	0.38	407	407	3.10	0.70
Lyles 2007[79] (HORIZON-RFT)	3	1	4	NA	NA	NA	NA	1062	1065	2.90	1.31
Black 2007[58] (HORIZON-PFT)	3	1	4	-0.04	5.06	0.16	0.15	3083	3067	5.06	0.15
Chesnut 2004[45] (BONE)	3	1	6	NA	NA	NA	NA	975	977	2.20	0.86
Rosen 2005[92] (FACT)	1	2	3	1.6	0.9	0.21	0.21	454	438	-0.70	0.28
Reid 2006[89] (FACTS)	1	2	3	2.25	1.67	0.18	0.18	424	430	-0.56	0.27

Vertebral fractures, random effects model.

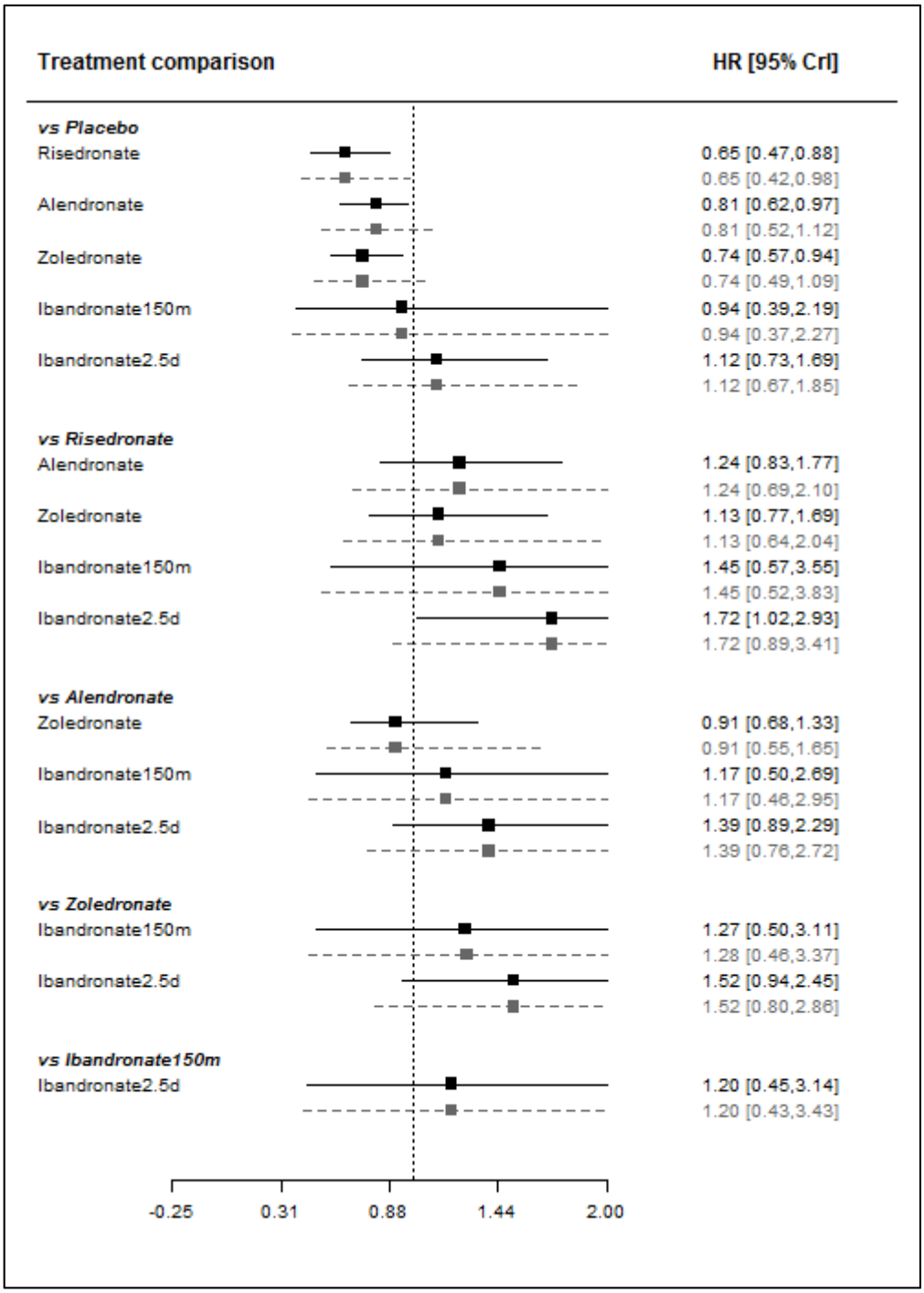
The model fitted the data well, with the total residual deviance of 42.17 being close to the total number of data points, 42, included in the analysis. The DIC was 72.50, suggesting a mild decline in model fit compared to the class effects model (DIC 69.28) . The between study standard deviation was estimated to be 0.20 (95% CrI: 0.02,0.57), implying mild heterogeneity in treatment effects between studies.



Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Non-vertebral fractures, random effects model

The model fitted the data well, with a total residual deviance of 22.78 being close to the total number of data points, 28, included in the analysis. The DIC was 43.47, suggesting a mild decline in model fit compared to the class effects model (DIC 42.32). The between study standard deviation was estimated to be 0.08 (95% CrI: 0.00, 0.35), implying mild heterogeneity in treatment effects between studies.

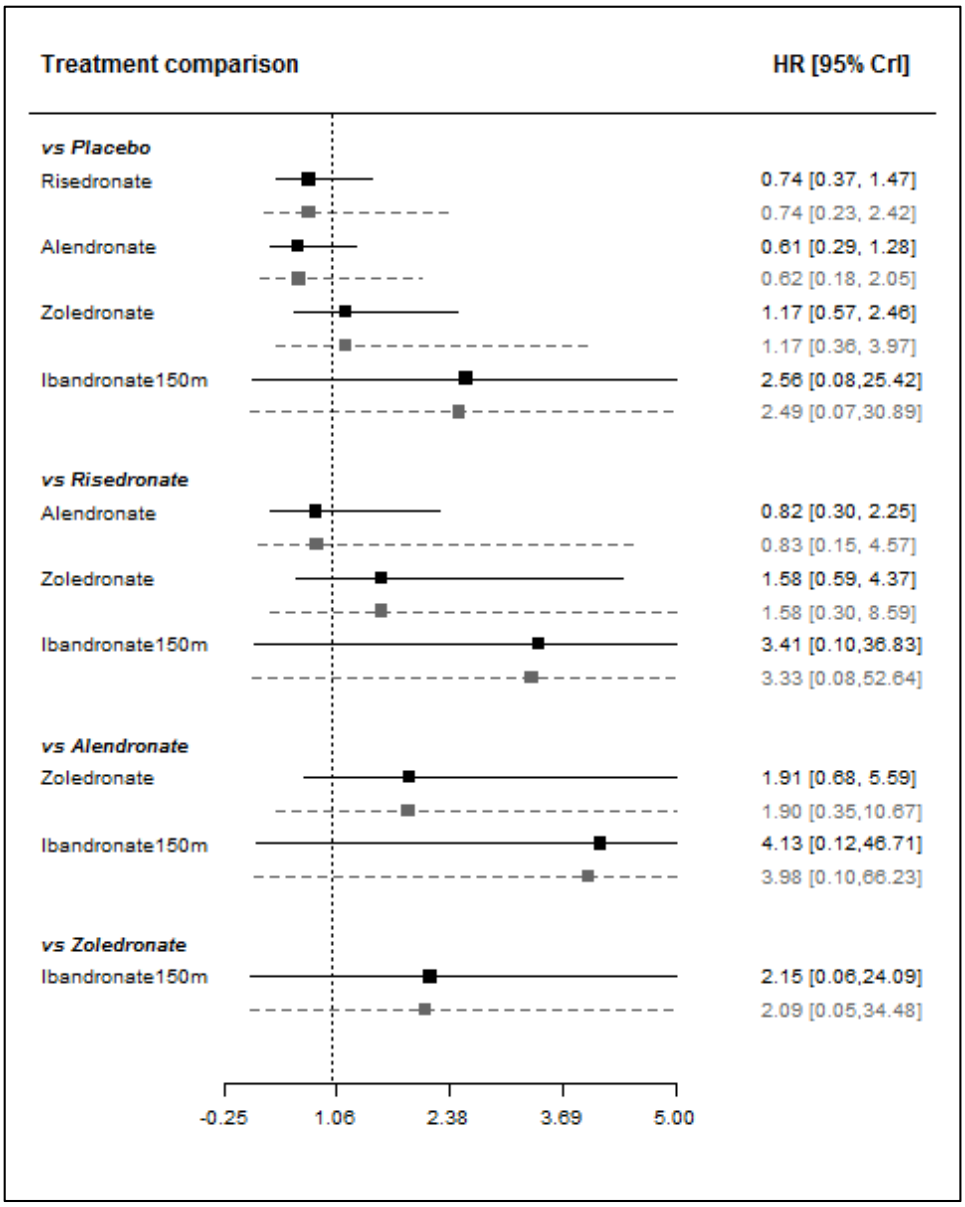


Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Hip fractures, random effects model

There were insufficient studies with which to estimate the between study standard deviation from the sample data alone and there were no events in the baseline treatment in the Lester 2008 study[76], which meant that the Marcov chain did not converge. In this case, a weakly informative prior distribution was used for the between study standard deviation such that $\tau \sim HN(0, 0.32^2)$ and weakly informative prior distribution for the study specific baseline of the Lester 2008 study [76] such that $\mu_i \sim N(-3.56, 0.59^2)$; this was generated by perfoming a random effects meta-analysis of the baselines from the other studies.

The model fitted the data well, with a total residual deviance of 17.73 being close to the total number of data points, 18, included in the analysis. The DIC was 33.61, suggesting little difference in model fit compared to the class effects model (DIC 33.82) . The between study standard deviation was estimated to be 0.44 (95% CrI: 0.23, 0.76), implying moderate heterogeneity between studies.

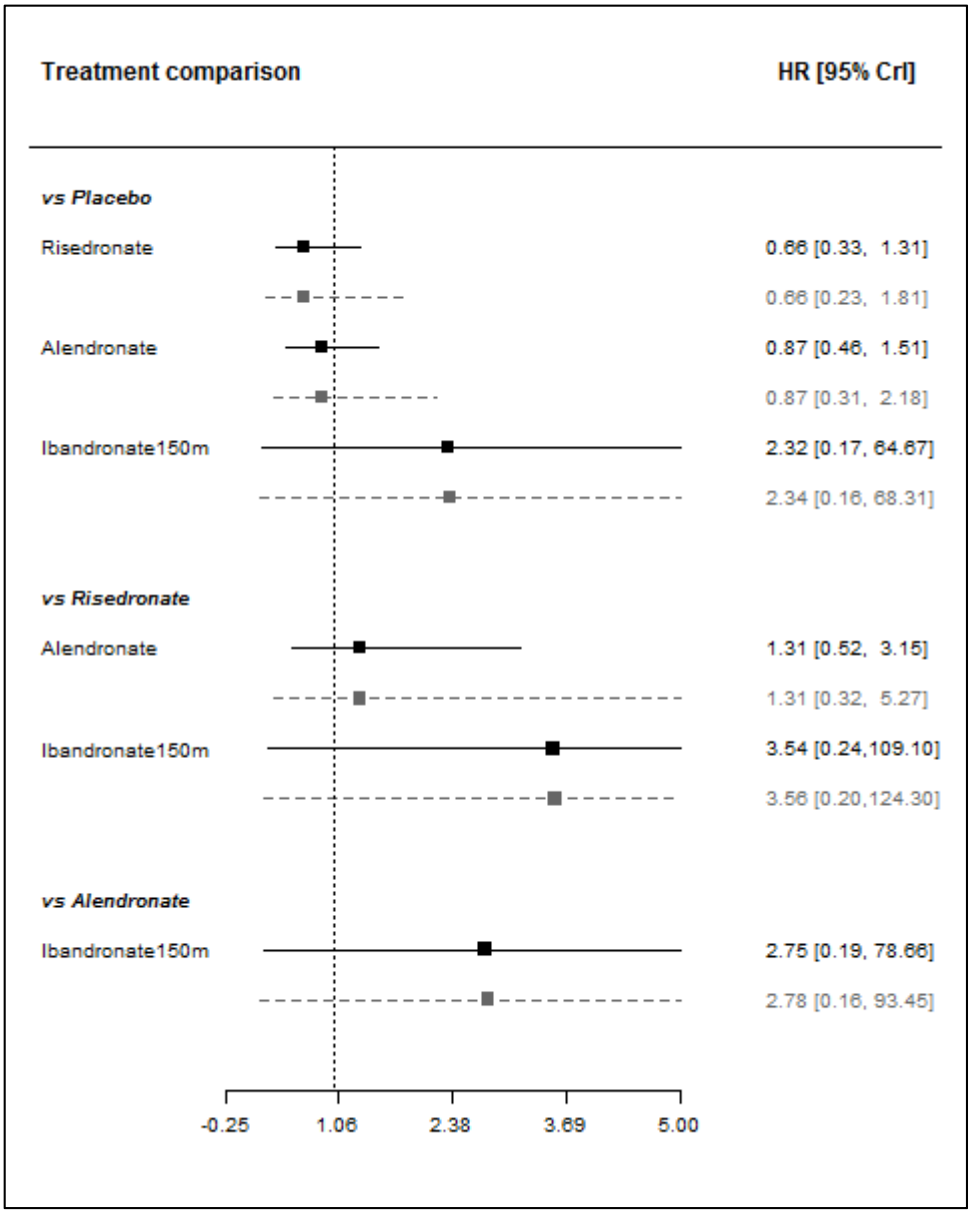


Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Wrist fractures, random effects model

There were insufficient studies with which to estimate the between study standard deviation from the sample data alone. In this case, a weakly informative prior distribution was used for the between study standard deviation such that $\tau \sim HN(0, 0.32^2)$.

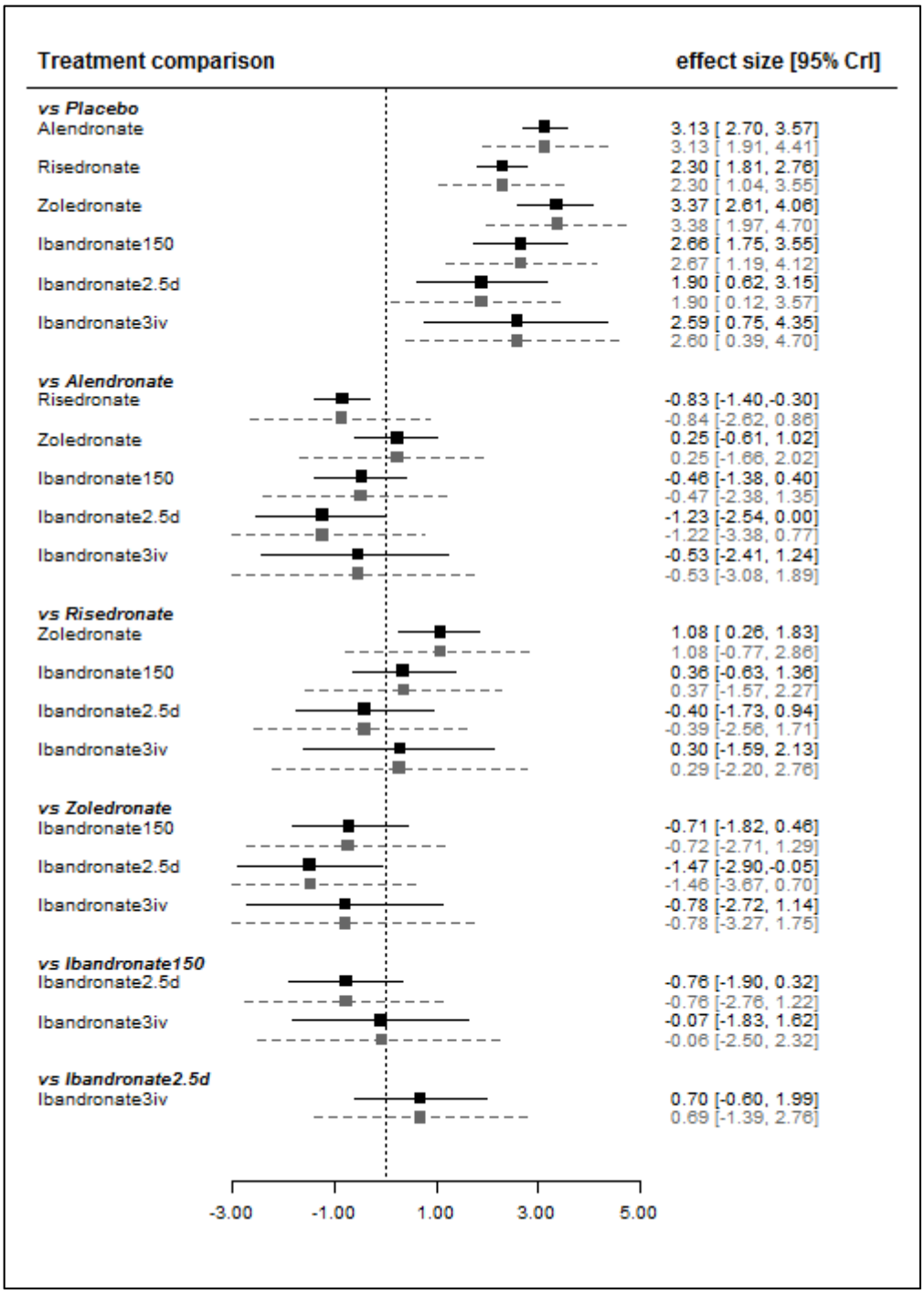
The model fitted the data well, with a total residual deviance, 13.88, being close to the total number of data points included in the analysis, 12. The DIC was 24.70, suggesting a mild decline in model fit compared to the class effects model (DIC 23.23). The between study standard deviation was estimated to be 0.30 (95% CrI: 0.03, 0.71), implying mild to moderate heterogeneity between studies.



Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Femoral neck BMD, random effects model

The model fitted the data well, with a total residual deviance of 55.30 being close to the total number of data points included in the analysis, 59. The DIC was 99.34, suggesting a mild decline in model fit compared to the class effects model (DIC 96.5). The between study standard deviation was estimated to be 0.55 (95% CrI: 0.31, 0.88), implying moderate heterogeneity between studies.

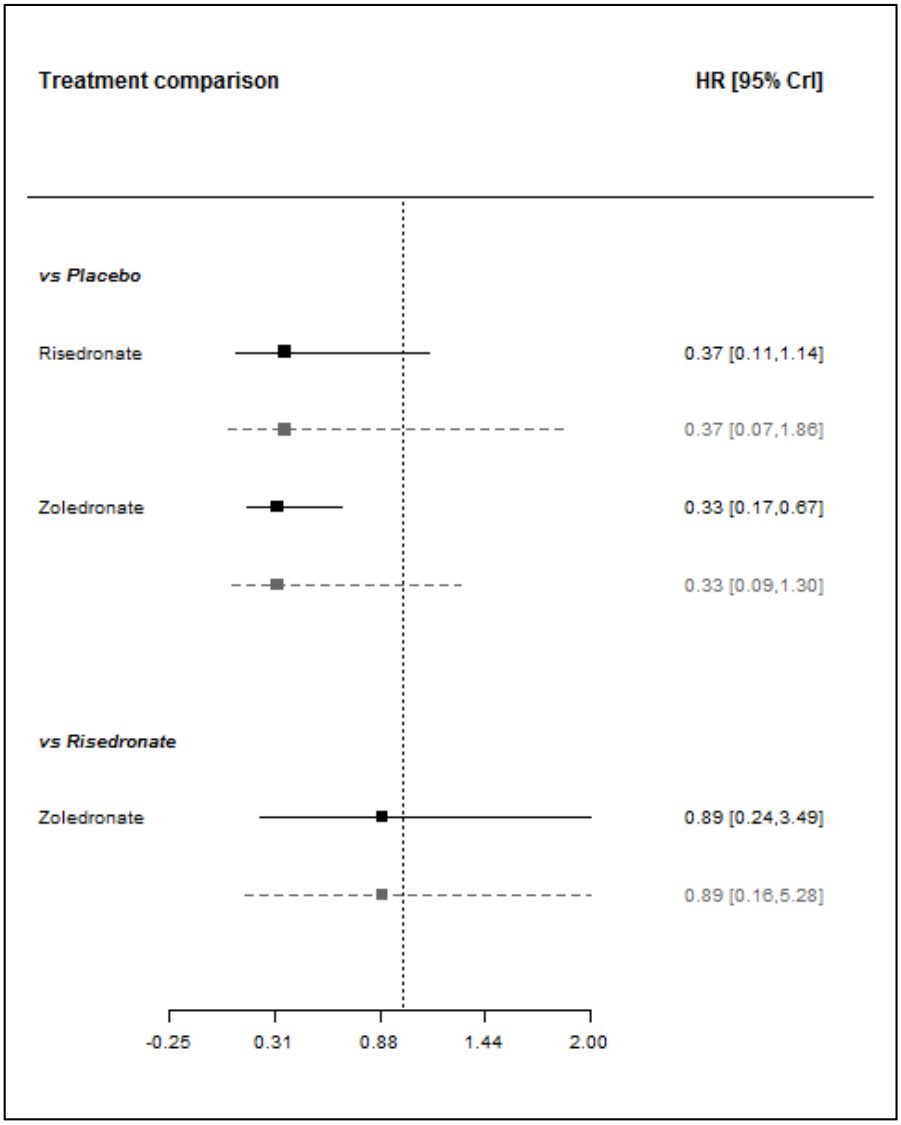


Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the right of the reference line favour the comparator treatment.

Clinical vertebral fractures, random effects model

There were insufficient studies with which to estimate the between study standard deviation from the sample data alone. In this case, a weakly informative prior distribution was used for the between study standard deviation such that $\tau \sim HN(0, 0.32^2)$.

The model fitted the data well, with a total residual deviance, 6.56, being close to the total number of data points included in the analysis, 6. The between study standard deviation was estimated to be 0.32 (95% CrI: 0.03, 0.78), which implies mild to moderate heterogeneity between studies.



Note: mean effect estimates are plotted in black; predictive effects in a new study are plotted in grey beneath. Treatment effects to the left of the reference line favour the comparator treatment.

Statistical model for the meta-analysis of placebo baselines.

To provide a suitable prior distribution for the study specific baseline of Lester 2008 [76], a random effects meta-analysis was performed on the placebo arms of all other studies. Again, the data generation process is assumed to follow a Binomial likelihood. i.e.

$$r_{ip} \sim bin(p_{ip}, n_{ip}),$$

where p_{ip} represents the probability of an event in the placebo arm of trial i ($i = 1 \ldots np$). For the hip fracture network, the number of studies with placebo baseline, np, is 8. The probabilities of fracture are modelled using the complementary log-log link function:

$$cloglog(p_{ip}) = \log(f_i) + \mu_i.$$

A random effects model is assumed, such that the trial-specific baselines are drawn from a Normal distribution with common mean and variance:

$$\mu_i \sim N(m, \tau_m^2).$$

To complete the model, common reference priors were assumed for the mean and variance: $\mu_i \sim N(0, 100^2)$ and $\tau_m^2 \sim U(0,2)$. The predictive distribution of a new baseline is given by

$$\mu_{new} \sim N(m, \tau_m^2).$$

Appendix 8: Table of excluded studies – cost-effectiveness review

Paper	Reason for exclusion
Jansen *et al.*, 2006[339]	Conference abstract
Not reported *et al.*, 2006[340]	Excluded interventions
Boonen *et al.*, 2009[341]	Systematic review
Botteman *et al.*, 2011[342]	Patients with renal cell carcinoma
Brandao *et al.*, 2012[343]	Systematic review
Cowell *et al.*, 2006[344]	Conference abstract
Dell *et al.*, 2010[345]	United States location
Fardellone *et al.*, 2007[346]	Conference abstract
Farquhar *et al.*, 2008[347]	Conference abstract
Grima *et al.*, 2008[348]	Conference abstract
Halperin *et al.*, 2006[349]	Conference abstract
Hiligsmann *et al.*, 2008[350]	Cost effectiveness of a pre-treatment scanning strategy
Hiligsmann *et al.*, 2007[351]	Conference abstract
Hiligsmann *et al.*, 2013[352]	Systematic review
Jansen *et al.*, 2006[353]	Conference abstract
Jansen *et al.*, 2008[354]	Excluded interventions
Johnell 1016[355]	Swedish location
Kanis *et al.*, 2011[356]	Systematic review
Kanis [357]	Excluded interventions
Kanis*et al.*, 2008[358]	Very limited discussion of modelling
Kanis *et al.*, 2008[359]	Response to a letter published previously in the same
Logman *et al.*, 2007[360]	Conference abstract
Logman *et al.*, 2009[361]	Conference poster
Logman *et al.*, 2008[362]	Conference abstract
Logman *et al.*, 2010[363]	Excluded intervention
Lynch *et al.*, 2007[364]	Conference abstract
Lynch *et al.*, 2006[365]	Conference abstract
Lynch *et al.*, 2007[366]	Conference abstract

McLellan *et al.*, 2011[367]	Cost-effectiveness assessment of methods of treatment
Olson *et al.*, 2007[368]	Conference abstract
Rizzoli *et al.*, 2011[369]	Systematic review
Rosenzweig *et al.*, 2009[370]	Review of osteoporosis, prevention & treatment, no
Simbula *et al.*, 2008[371]	Full text paper not in the English language
Stevenson *et al.*, 2009[372]	Establishing optimum duration of treatment
Stevenson *et al.*, 2011[373]	Excluded interventions
Sunyecz *et al.*, 2008[374]	Conference abstract
Warde *et al.*, 2010[375]	In brief article

Appendix 9: Parameter distributions used in the probabilistic sensitivity analysis

Table 39: Distributions assigned to the parameters used in the model

Parameter description	Distribution	Mean	Standard error	Parameter 1	Parameter 2	Source(s)
Patients hospitalized						
Following vertebral fracture	Beta	0.40	n/a	587	884	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.29	n/a	2081	4989	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.35	n/a	894	1651	Gutierrez *et al.* [252]
Following hip fracture	Fixed	1.00	n/a	n/a	n/a	Gutierrez *et al.* [251]
Accident & emergency visits						
Following vertebral fracture	Beta	0.11	n/a	171	1300	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.21	n/a	1489	5581	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.18	n/a	469	2076	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.18	n/a	442	1985	Gutierrez *et al.* [251]
GP visits						
Following vertebral fracture	Beta	0.97	n/a	1425	46	Gutierrez *et al.* [252]

Following wrist or forearm fracture	Beta	0.95	n/a	6689	381	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.94	n/a	2385	160	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.88	n/a	2141	286	Gutierrez *et al.* [251]
Referral visits						
Following vertebral fracture	Beta	0.50	n/a	730	741	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.37	n/a	2623	4447	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.34	n/a	875	1670	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.33	n/a	805	1622	Gutierrez *et al.* [251]
Patient deaths						
Following vertebral fracture	Beta	0.09	n/a	131	1340	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.04	n/a	271	6799	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.07	n/a	197	2348	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.08	n/a	197	2230	Gutierrez *et al.* [251]
Patients with a prior fracture						

Patients hospitalized						
Following vertebral fracture	Beta	0.17	n/a	245	1226	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.13	n/a	895	6175	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.15	n/a	383	2162	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.18	n/a	432	1995	Gutierrez *et al.* [251]
Accident & emergency visits						
Following vertebral fracture	Beta	0.04	n/a	64	1407	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.03	n/a	208	6862	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.03	n/a	82	2463	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.04	n/a	95	2332	Gutierrez *et al.* [251]
GP visits						
Following vertebral fracture	Beta	0.90	n/a	1319	152	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.89	n/a	6268	802	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.91	n/a	2305	240	Gutierrez *et al.* [252]

Following hip fracture	Beta	0.91	n/a	2200	227	Gutierrez *et al.* [251]
Referral visits						
Following vertebral fracture	Beta	0.32	n/a	475	996	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.28	n/a	1988	5082	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.29	n/a	749	1796	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.32	n/a	775	1652	Gutierrez *et al.* [251]
Patient deaths						
Following vertebral fracture	Beta	0.05	n/a	78	1393	Gutierrez *et al.* [252]
Following wrist or forearm fracture	Beta	0.04	n/a	252	6818	Gutierrez *et al.* [252]
Following humerus fracture	Beta	0.04	n/a	104	2441	Gutierrez *et al.* [252]
Following hip fracture	Beta	0.04	n/a	104	2323	Gutierrez *et al.* [251]
Difference in medications prescribed between patients with a previous fracture and those without						
Following vertebral fracture	Normal	22.35	2.16	22.35	2.16	Gutierrez *et al.* [252]

Following wrist or forearm fracture	Normal	4.61	0.61	4.61	0.61	Gutierrez *et al.* [252]
Following humerus fracture	Normal	4.61	0.61	4.61	0.61	Gutierrez *et al.* [252]
Following hip fracture	Normal	12.34	1.72	12.34	1.72	Gutierrez *et al.* [251]
Utility multipliers in year of fracture						
Hip fracture	Beta	0.69	0.016	575.84	258.71	Strom *et al.* [244]
Vertebral fracture	Beta	0.57	0.035	113.48	85.61	Strom *et al.* [244]
Humerus fracture	Beta	0.86	0.085	13.47	2.19	Strom *et al.* [244]
Wrist or forearm fracture	Beta	0.88	0.015	412.13	56.20	Zethraeus, 2002 [238]
Utility multiplier in subsequent years						
Hip fracture	Beta	0.85	0.016	422.49	74.56	Strom *et al.* [244]
Vertebral fracture	Beta	0.66	0.035	120.24	61.94	Strom *et al.* [244]
Humerus fracture	Fixed	1.00	n/a	n/a	n/a	Zethraeus, 2002 [238]
Wrist or forearm fracture	Beta	0.98	0.015	84.39	1.72	Strom *et al.* [244]
Patient admitted to nursing home	Beta	0.63	0.191	3.38	2.03	Tidermark *et al.* [243]
Life expectancy for patient suffering a fatal hip fracture	Fixed	0.25	n/a	n/a	n/a	Assumption
Relative risk of mortality following hip fracture for patients admitted to a nursing	Log-normal	0.57	0.074	-0.56212	0.13150	Smith 2014 [174]

home						
Duration of treatment (years)						
Alendronate	Normal	0.504	0.028	0.504	0.028	Imaz *et al.* [187]
Risedronate	Normal	0.504	0.028	0.504	0.028	Imaz *et al.* [187]
Ibandronate (oral preparation)	Normal	0.504	0.028	0.504	0.028	Imaz *et al.* [187]
Ibandronate (IV preparation)	Normal	1.100	0.041	1.100	0.041	Curtis 2012[189]
Zoledronate	Normal	1.700	0.018	1.700	0.018	Curtis [189] 2012
Annual cost of treatment						
Alendronate	Fixed	£14.73	n/a	n/a	n/a	Drug Tariff [255]
Risedronate	Fixed	£16.43	n/a	n/a	n/a	Drug Tariff [255]
Ibandronate (oral preparation)	Fixed	£13.58	n/a	n/a	n/a	Drug Tariff [255]
Ibandronate (IV preparation)	Fixed	£221.52	n/a	n/a	n/a	eMIT[42]
Zoledronate	Fixed	£339.67	n/a	n/a	n/a	eMIT[42]
Acute costs of fracture						
Hip fracture	See detailed breakdown in tables 9.7 to 9.13 of Appendix 9	£6,160.88	n/a	n/a	n/a	-
Vertebral fracture		£945.97	n/a	n/a	n/a	-
Humerus fracture		£1,063.08	n/a	n/a	n/a	-
Wrist or forearm fracture		£702.61	n/a	n/a	n/a	-
Annual chronic costs of fracture						
Hip fracture	Fixed	£112.39	n/a	n/a	n/a	Guiterrez *et al.*[251]
Vertebral fracture	Fixed	£339.28	n/a	n/a	n/a	Guiterrez *et al.*

						[252]
Humerus fracture	Fixed	£71.02	n/a	n/a	n/a	Guiterrez *et al.* [252]
Wrist or forearm fracture	Fixed	£71.02	n/a	n/a	n/a	Guiterrez *et al.* [252]
Patient admitted to nursing home	Fixed	£36,608.00	n/a	n/a	n/a	Curtis [27]
Fracture associated home help costs						
Hip fracture	Fixed	£1,729.44	n/a	n/a	n/a	Curtis [27]
Vertebral fracture	Fixed	£2,651.10	n/a	n/a	n/a	Curtis [27]
Humerus fracture	Fixed	£131.74	n/a	n/a	n/a	Curtis [27]
Wrist or forearm fracture	Fixed	£131.74	n/a	n/a	n/a	Curtis [27]

Table 40: Distributions used in the probabilistic sensitivity analysis for the increased risk of fracture following incident fracture

Description	Distribution	Midpoint	Standard error	Parameter 1	Parameter 2	Source(s)
HR for future hip fracture given:						
Prior hip fracture	Log-normal	2.3	0.561	0.832909	0.230323	Klotzbuecher *et al.* [228]
Prior vertebral facture	Log-normal	2.3	0.204	0.832909	0.085835	Klotzbuecher *et al.* [228]
Prior humerus fracture	Log-normal	2.0	0.077	0.693147	0.037399	Klotzbuecher *et al.* [228]
Prior wrist/forearm fracture	Log-normal	1.9	0.153	0.641854	0.081238	Klotzbuecher *et al.* [228]
HR for future vertebral fracture given:						
Prior hip fracture	Log-normal	2.5	0.434	0.916291	0.169637	Klotzbuecher *et al.* [228]
Prior vertebral facture	Log-normal	4.4	0.459	1.481605	0.103435	Klotzbuecher *et al.* [228]
Prior humerus fracture	Log-normal	2.0	0.204	0.693147	0.103435	Klotzbuecher *et al.* [228]
Prior wrist/forearm fracture	Log-normal	1.7	0.179	0.530628	0.103435	Klotzbuecher *et al.* [228]
HR for future humerus fracture given:						
Prior hip fracture	Log-normal	2.1	4.337	0.741937	1.034357	Warriner *et al.* [231]
Prior vertebral facture	Log-normal	1.6	0.587	0.470004	0.371247	Warriner *et al.*

						[231]
Prior humerus fracture	Log-normal	2.1	4.337	0.741937	1.034357	Klotzbuecher *et al.* [228]
Prior wrist/forearm fracture	Log-normal	2.5	2.449	0.916291	0.722759	Warriner *et al.* [231]
HR for future wrist/forearm fracture given:						
Prior hip fracture	Log-normal	3.0	1.327	1.098612	0.410571	Warriner *et al.* [231]
Prior vertebral facture	Log-normal	1.4	0.128	0.336472	0.088854	Klotzbuecher *et al.* [228]
Prior humerus fracture	Log-normal	1.9	0.383	0.641854	0.195728	Klotzbuecher *et al.* [228]
Prior wrist/forearm fracture	Log-Normal	3.3	0.383	1.193922	0.142759	Klotzbuecher *et al.* [228]

Table 41 Distributions used in the probabilistic sensitivity analysis for the probability of mortality following hip fracture

Description	Distribution	Mean	Standard error	Parameter 1	Parameter 2	Source(s)
Female patients						
Age 30 – 39 Years	Fixed	0.000	n/a	n/a	n/a	Van Staa *et al.* [158]
Age 40 – 49 Years	Fixed	0.000	n/a	n/a	n/a	Van Staa *et al.* [158]
Age 50 – 59 Years	Beta	0.024	n/a	21.649	880.386	Van Staa *et al.* [158]
Age 60 – 69 Years	Beta	0.044	n/a	109.383	2376.587	Van Staa *et al.* [158]
Age 70 – 79 Years	Beta	0.075	n/a	301.095	3713.504	Van Staa *et al.* [158]
Age 80 – 89 Years	Beta	0.114	n/a	433.698	3370.667	Van Staa *et al.* [158]
Age 90 – 99 Years	Beta	0.136	n/a	139.921	888.912	Van Staa *et al.* [160]
Male patients						
Age 30 – 39 Years	n/a	0.000	n/a	n/a	n/a	-
Age 40 – 49 Years	n/a	0.000	n/a	n/a	n/a	-
Age 50 – 59 Years	n/a	0.037	n/a	n/a	n/a	-
Age 60 – 69 Years	n/a	0.072	n/a	n/a	n/a	-
Age 70 – 79 Years	n/a	0.134	n/a	n/a	n/a	-

Age 80 – 89 Years	n/a	0.181	n/a	n/a	n/a	-
Age 90 – 99 Years	n/a	0.200	n/a	n/a	n/a	-

Note: For male patients the values sampled for female patients are multiplies by a gender mortality ratio taken from Roberts[209]

Table 42 Distributions used in the probabilistic sensitivity analysis for the probability of nursing home admission following fracture

Description	Distribution	Mean	Standard error	Parameter 1	Parameter 2	Source(s)
Overall rate of new admission to nursing home across all ages and gender	beta	20%	n/a	274	1370	Najayan, 2014[225]
Age 30 – 39 Years	Calculated from overall rate which is sampled (see row above)	0.000	n/a	n/a	n/a	Najayan 2014[225]
Age 40 – 49 Years		0.000	n/a	n/a	n/a	Najayan 2014[225]
Age 50 – 59 Years		0.035	n/a	n/a	n/a	Najayan 2014[225]
Age 60 – 69 Years		0.064	n/a	n/a	n/a	Najayan 2014[225]
Age 70 – 79 Years		0.113	n/a	n/a	n/a	Najayan 2014[225]
Age 80 – 89 Years		0.192	n/a	n/a	n/a	Najayan 2014[225]
Age 90 – 99 Years		0.307	n/a	n/a	n/a	Najayan 2014[225]
Male patients						
Age 30 – 39 Years	Calculated from overall rate which is sampled (see row above)	0.000	n/a	n/a	n/a	Najayan 2014[225]
Age 40 – 49 Years		0.000	n/a	n/a	n/a	Najayan 2014[225]
Age 50 – 59 Years		0.057	n/a	n/a	n/a	Najayan 2014[225]
Age 60 – 69 Years		0.102	n/a	n/a	n/a	Najayan 2014[225]
Age 70 – 79 Years		0.175	n/a	n/a	n/a	Najayan 2014[225]

Age 80 – 89 Years		0.284	n/a	n/a	n/a	Najayan 2014[225]
Age 90 – 99 Years		0.425	n/a	n/a	n/a	Najayan 2014[225]

Table 43 Distributions used in the probabilistic sensitivity analysis for the probability of mortality following vertebral fracture

Description	Distribution	Mean	Standard error	Parameter 1	Parameter 2	Source(s)
All patients						
Age 30 – 39 Years	Fixed	0.000	n/a	n/a	n/a	Van Staa *et al.* [158]
Age 40 – 49 Years	Fixed	0.000	n/a	n/a	n/a	Van Staa *et al.* [158]
Age 50 – 59 Years	Beta	0.023	n/a	85.581	3635.314	Van Staa *et al.* [158]
Age 60 – 69 Years	Beta	0.035	n/a	247.105	6813.048	Van Staa *et al.* [158]
Age 70 – 79 Years	Beta	0.052	n/a	378.597	6902.117	Van Staa *et al.* [158]
Age 80 – 89 Years	Beta	0.067	n/a	285.369	3973.865	Van Staa *et al.* [158]
Age 90 – 99 Years	Beta	0.066	n/a	53.757	760.736	Van Staa *et al.* [158]

Table 44: Distributions used in the probabilistic sensitivity analysis for accident and emergency treatment in the year after fracture

Service Code	Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
T02A	VB07Z	34,920	£94	£28	Gamma	382,885.49	0.0002
T02NA	VB07Z	24,835	£82	£39	Gamma	109,477.62	0.0007

Source was 2013/14 NHS Reference costs[256]

Table 45: Distributions used in the probabilistic sensitivity analysis for referrals in the year after fracture .

Service Code	Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
WF01B	302	109,162	£186.54	£66	Gamma	955.04	0.20
WF01A	302	353,215	£133.00	£47	Gamma	989.53	0.13

Source was 2013/14 NHS Reference costs[256]

Table 46: Distributions used in the probabilistic sensitivity analysis for hospitalisation for humerus fracture in the year after fracture

Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
Procedure						

HA61B	951	£7,194	£1,931	Gamma	1,943.78	3.7
HA61C	1,880	£4,305	£1,270	Gamma	1,618.63	2.66
HA62Z	249	£3,654	£1,613	Gamma	549.10	6.65
HA63Z	611	£2,520	£944	Gamma	947.75	2.66
HA69Z	1	£323	n/a	Fixed	n/a	n/a
Excess bed day						
HA61B	1,622	£276.43	£110	Gamma	421.63	0.66
HA61C	3,010	£312.62	£89	Gamma	1,607.77	0.19
HA62Z	1,158	£294.37	£114	Gamma	380.05	0.77
HA63Z	2,155	£244.89	£86	Gamma	800.88	0.31

Source was 2013/14 NHS Reference costs[256]

Table47: Distributions used in the probabilistic sensitivity analysis for hospitalisation for wrist fracture in the year after fracture

Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
Procedure						
HA71B	1,356	£3,835	£1,196	Gamma	186.41	7.27
HA71C	7,494	£2,913	£888	Gamma	10,408.22	0.72
HA72Z	845	£2,585	£1,026	Gamma	87.52	9.66
HA73B	869	£1,637	£492	Gamma	369.14	2.19
HA73C	963	£1,481	£704	Gamma	254.31	3.79
HA79Z	1	£371	n/a	Fixed	n/a	n/a
Excess bed day						
HA71B	2,475	£291	£88	Gamma	993.96	0.29
HA71C	3,716	£314	£120	Gamma	974.53	0.32
HA72Z	975	£256	£101	Gamma	531.39	0.48
HA73B	110	£379	£144	Gamma	152.54	2.48
HA73C	2,703	£265	£93	Gamma	943.70	0.28

Source was 2013/14 NHS Reference costs[256]

Table 48: Distributions used in the probabilistic sensitivity analysis for hospitalisation for hip fracture (procedure costs) in the year after fracture

Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
Procedure						
HA11A	713	£13,408	£4,678	Gamma	1,117.05	12.00
HA11B	319	£8,791	£3,503	Gamma	680.27	12.92
HA11C	773	£7,337	£1,847	Gamma	2,051.83	3.58
HA12B	19,080	£8,210	£1,786	Gamma	3,064.35	2.68
HA12C	9,890	£6,417	£1,159	Gamma	4,507.56	1.42
HA13A	10,212	£8,237	£1,997	Gamma	2,415.09	3.41
HA13B	5,355	£6,570	£1,726	Gamma	2,057.28	3.19
HA13C	9,673	£5,551	£1,129	Gamma	3,528.05	1.57
HA14A	249	£7,312	£3,737	Gamma	398.07	18.37
HA14B	216	£4,905	£2,020	Gamma	595.70	8.23
HA14C	645	£3,939	£1,064	Gamma	1,904.04	2.07
HA19Z	1	£7,790	n/a	Fixed	n/a	n/a

Source was 2013/14 NHS Reference costs[256]

Table 49: Distributions used in the probabilistic sensitivity analysis for hospitalisation for hip fracture (excess bed day costs) in the year after fracture

Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
Excess bed day						
HA11A	1,404	£312	£84	Gamma	410.74	0.76
HA11B	307	£299	£115	Gamma	177.30	1.69
HA11C	394	£311	£89	Gamma	296.08	1.05
HA12B	16,310	£282	£88	Gamma	1,376.53	0.20
HA12C	4,463	£267	£98	Gamma	886.70	0.30
HA13A	8,630	£290	£88	Gamma	1,176.62	0.25
HA13B	2,502	£292	£95	Gamma	746.43	0.39
HA13C	3,674	£262	£69	Gamma	1,715.15	0.15
HA14A	466	£256	£120	Gamma	86.67	2.95
HA14B	198	£339	£226	Gamma	45.04	7.53
HA14C	962	£317	£159	Gamma	232.60	1.37

Source was 2013/14 NHS Reference costs[256]

Table 50: Distributions used in the probabilistic sensitivity analysis for vertebral fracture hospitalisations in the year after fracture.

Currency Code	Number of patients treated	Mean unit cost	Standard deviation	Distribution	Parameter 1	Parameter 2
Procedure						
HC20D	1,609	£5,479	£2,858	Gamma	543.85	10.07
HC20E	2,459	£3,732	£1,648	Gamma	758.57	4.92
HC20F	2,611	£2,971	£1,136	Gamma	1,031.87	2.88
HC20G	1,904	£2,265	£646	Gamma	1,806.58	1.25
Excess bad day						
HC20D	2,317	£328.19	£128	Gamma	347.54	0.94
HC20E	3,772	£260.82	£125	Gamma	393.07	0.66
HC20F	2,363	£266.99	£76	Gamma	1,171.35	0.23
HC20G	2,047	£282.03	£117	Gamma	599.23	0.47

Source was 2013/14 NHS Reference costs[256]

Appendix 10: Parameter distributions used in the probabilistic sensitivity analysis

Table 51 Basecase results from 200,000 PSA samples for QFracture risk category 1

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£827.18	15.88153	£0.00	0.00000	NA	£316,803	£475,619	NA
Ibandronate (oral)	£834.63	15.88164	£7.45	0.00011	£67,340	£316,798	£475,615	£67,340
Alendronate	£835.01	15.88164	£7.83	0.00011	£68,204	£316,798	£475,614	£91,325
Risedronate	£835.96	15.88157	£8.78	0.00004	£219,757	£316,795	£475,611	Dominated
Ibandronate (i.v.)	£1,053.14	15.88123	£225.96	-0.00030	-£757,885	£316,571	£475,384	Dominated
Zoledronate (i.v.)	£1,385.41	15.88196	£558.24	0.00043	£1,301,875	£316,254	£475,073	£1,752,783

*ICER versus next least costly non-dominated strategy

Table 52: Basecase results from 200,000 PSA samples for QFracture risk category 2

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£1,532.33	14.74097	£0.00	0.00000	NA	£293,287	£440,697	NA
Ibandronate (oral)	£1,539.62	14.74105	£7.29	0.00008	£96,451	£293,281	£440,692	Extendedly dominated
Alendronate	£1,540.17	14.74108	£7.84	0.00010	£76,943	£293,281	£440,692	Extendedly dominated
Risedronate	£1,540.77	14.74110	£8.44	0.00013	£65,692	£293,281	£440,692	£65,692
Ibandronate (i.v.)	£1,757.78	14.74075	£225.45	-0.00023	-£997,490	£293,057	£440,465	Dominated
Zoledronate (i.v.)	£2,088.19	14.74166	£555.86	0.00068	£813,849	£292,745	£440,162	£987,243

*ICER versus next least costly non-dominated strategy

Table 53: Basecase results from 200,000 PSA samples for QFracture risk category 3

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£2,971.75	13.55783	£0.00	0.00000	NA	£268,185	£403,763	NA
Risedronate	£2,977.17	13.55813	£5.42	0.00030	£17,906	£268,185	£403,767	£17,906
Alendronate	£2,979.29	13.55813	£7.54	0.00030	£24,867	£268,183	£403,765	Extendedly dominated
Ibandronate (oral)	£2,979.64	13.55808	£7.89	0.00025	£31,440	£268,182	£403,763	Dominated
Ibandronate (i.v.)	£3,196.69	13.55889	£224.94	0.00106	£213,067	£267,981	£403,570	£291,495
Zoledronate (i.v.)	£3,520.69	13.55932	£548.94	0.00150	£367,160	£267,666	£403,259	£737,415

*ICER versus next least costly non-dominated strategy

Table 54: Basecase results from 200,000 PSA samples for QFracture risk category 4

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£3,881.90	12.32917	£0.00	0.00000	NA	£242,702	£365,993	NA
Alendronate	£3,886.67	12.32946	£4.77	0.00028	£16,820	£242,702	£365,997	£16,820
Ibandronate (oral)	£3,888.83	12.32930	£6.93	0.00012	£55,519	£242,697	£365,990	Dominated
Risedronate	£3,889.93	12.32945	£8.02	0.00027	£29,255	£242,699	£365,994	Dominated
Ibandronate (i.v.)	£4,106.75	12.32927	£224.84	0.00009	£2,444,347	£242,479	£365,771	Dominated
Zoledronate (i.v.)	£4,436.61	12.33057	£554.71	0.00140	£397,032	£242,175	£365,481	£493,762

*ICER versus next least costly non-dominated strategy

Table 55: Basecase results from 200,000 PSA samples for QFracture risk category 5

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£4,052.25	11.42224	£0.00	0.00000	NA	£224,393	£338,615	NA
Alendronate	£4,059.38	11.42235	£7.13	0.00010	£68,244	£224,388	£338,611	£68,244
Ibandronate (oral)	£4,060.12	11.42216	£7.86	-0.00008	-£98,972	£224,383	£338,605	Dominated
Risedronate	£4,065.83	11.42228	£13.58	0.00003	£415,596	£224,380	£338,602	Dominated
Ibandronate (i.v.)	£4,276.53	11.42247	£224.28	0.00022	£997,367	£224,173	£338,398	Extendedly dominated
Zoledronate (i.v.)	£4,604.88	11.42422	£552.63	0.00198	£279,227	£223,880	£338,122	£290,988

*ICER versus next least costly non-dominated strategy

Table56: Basecase results from 200,000 PSA samples for QFracture risk category 6

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£4,371.39	10.40268	£0.00	0.00000	NA	£203,682	£307,709	NA
Alendronate	£4,374.47	10.40301	£3.08	0.00032	£9,468	£203,686	£307,716	£9,468
Risedronate	£4,378.91	10.40296	£7.52	0.00028	£27,166	£203,680	£307,710	Dominated
Ibandronate (oral)	£4,379.07	10.40298	£7.67	0.00029	£26,208	£203,680	£307,710	Dominated
Ibandronate (i.v.)	£4,603.74	10.40323	£232.35	0.00055	£421,634	£203,461	£307,493	Extendedly dominated
Zoledronate (i.v.)	£4,916.96	10.40474	£545.57	0.00206	£265,440	£203,178	£307,225	£313,498

*ICER versus next least costly non-dominated strategy

Table 57: Basecase results from 200,000 PSA samples for QFracture risk category 7

	Mean outcomes (discounted)		Incremental outcomes versus no treatment (discounted)		ICER vs. no treatment	Net benefit at £20K per QALY	Net benefit at £30K per QALY	Incremental analysis
Treatment strategy	Cost	QALYs	Cost	QALYs				
Risedronate	£4,584.47	9.38541	-£0.57	0.00047	-£1,213	£183,124	£276,978	NA
Alendronate	£4,584.52	9.38539	-£0.52	0.00045	-£1,152	£183,123	£276,977	Dominated
No treatment	£4,585.04	9.38494	£0.00	0.00000	NA	£183,114	£276,963	Dominated
Ibandronate (oral)	£4,590.32	9.38526	£5.28	0.00032	£16,705	£183,115	£276,967	Dominated
Ibandronate (i.v.)	£4,806.39	9.38577	£221.35	0.00083	£267,841	£182,909	£276,767	Extendedly dominated
Zoledronate (i.v.)	£5,136.10	9.38814	£551.06	0.00320	£172,324	£182,627	£276,508	£202,041

*ICER versus next least costly non-dominated strategy

Table 58: Basecase results from 200,000 PSA samples for QFracture risk category 8

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
Risedronate	£5,603.84	8.33619	-£4.24	0.00067	-£6,287	£161,120	£244,482	NA
Alendronate	£5,607.53	8.33657	-£0.55	0.00106	-£515	£161,124	£244,490	£9,563
No treatment	£5,608.08	8.33551	£0.00	0.00000	NA	£161,102	£244,457	Dominated
Ibandronate (oral)	£5,616.53	8.33618	£8.45	0.00066	£12,715	£161,107	£244,469	Dominated
Ibandronate (i.v.)	£5,837.84	8.33648	£229.77	0.00097	£237,905	£160,892	£244,256	Dominated
Zoledronate (i.v.)	£6,157.62	8.33899	£549.54	0.00348	£157,893	£160,622	£244,012	£227,376

*ICER versus next least costly non-dominated strategy

Table 59: Basecase results from 200,000 PSA samples for QFracture risk category 9

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis**
Treatment strategy	Cost	QALYs	Cost	QALYs				
Alendronate	£8,678.06	6.51525	-£10.66	0.00114	-£9,322	£121,627	£186,780	NA
Risedronate	£8,680.76	6.51549	-£7.97	0.00138	-£5,791	£121,629	£186,784	£11,621
Ibandronate (oral)	£8,688.18	6.51507	-£0.54	0.00096	-£563	£121,613	£186,764	Dominated
No treatment	£8,688.72	6.51411	£0.00	0.00000	NA	£121,594	£186,735	Dominated
Ibandronate (i.v.)	£8,902.45	6.51557	£213.72	0.00146	£146,407	£121,409	£186,565	Extendedly dominated
Zoledronate (i.v.)	£9,221.00	6.51944	£532.28	0.00533	£99,907	£121,168	£186,362	£136,695

*ICER versus next least costly non-dominated strategy

Table 60: Basecase results from 200,000 PSA samples for QFracture risk category 10

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Risedronate	£19,576.95	4.01080	-£17.24	0.00118	-£14,610	£60,639	£100,747	NA
Alendronate	£19,587.52	4.01086	-£6.67	0.00124	-£5,392	£60,630	£100,738	£188,505
No treatment	£19,594.19	4.00962	£0.00	0.00000	NA	£60,598	£100,695	Dominated
Ibandronate (oral)	£19,624.63	4.01018	£30.44	0.00055	£54,995	£60,579	£100,681	Dominated
Ibandronate (i.v.)	£19,840.81	4.01059	£246.62	0.00096	£255,998	£60,371	£100,477	Dominated
Zoledronate (i.v.)	£20,137.69	4.01250	£543.50	0.00288	£189,028	£60,112	£100,237	£335,702

*ICER versus next least costly non-dominated strategy

Appendix 11: Parameter distributions used in the probabilistic sensitivity analysis

Table 61 Basecase results from 200,000 PSA samples for FRAX risk category 1

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£5,838.92	13.56127	£0.00	0.00000	NA	£265,387	£400,999	NA
Alendronate	£5,841.54	13.56248	£2.62	0.00121	£2,175	£265,408	£401,033	£2,175
Risedronate	£5,842.90	13.56252	£3.98	0.00125	£3,197	£265,408	£401,033	£34,124
Ibandronate (oral)	£5,844.50	13.56216	£5.57	0.00089	£6,268	£265,399	£401,020	Dominated
Ibandronate (i.v.)	£6,060.14	13.56305	£221.22	0.00177	£124,931	£265,201	£400,831	Extendedly dominated
Zoledronate (i.v.)	£6,394.34	13.56640	£555.41	0.00512	£108,395	£264,934	£400,598	£141,073

*ICER versus next least costly non-dominated strategy

Table 62: Basecase results from 200,000 PSA samples for FRAX risk category 2

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Risedronate	£5,863.60	13.24259	-£10.18	0.00140	-£7,272	£258,988	£391,414	NA
Ibandronate (oral)	£5,873.38	13.24252	-£0.40	0.00133	-£300	£258,977	£391,402	Dominated
No treatment	£5,873.78	13.24119	£0.00	0.00000	NA	£258,950	£391,362	Dominated
Alendronate	£5,875.18	13.24287	£1.40	0.00168	£835	£258,982	£391,411	£41,144
Ibandronate (i.v.)	£6,089.91	13.24364	£216.14	0.00245	£88,127	£258,783	£391,219	Extendedly dominated
Zoledronate (i.v.)	£6,401.88	13.24829	£528.10	0.00710	£74,347	£258,564	£391,047	£97,132

*ICER versus next least costly non-dominated strategy

Table 63: Basecase results from 200,000 PSA samples for FRAX risk category 3

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Risedronate	£6,324.67	13.33625	-£6.81	0.00176	-£3,879	£260,400	£393,763	NA
Ibandronate (oral)	£6,330.04	13.33636	-£1.44	0.00186	-£775	£260,397	£393,761	Extendedly dominated
No treatment	£6,331.48	13.33450	£0.00	0.00000	NA	£260,358	£393,703	Dominated
Alendronate	£6,333.01	13.33660	£1.53	0.00211	£727	£260,399	£393,765	£23,752
Ibandronate (i.v.)	£6,549.59	13.33764	£218.11	0.00314	£69,413	£260,203	£393,580	Extendedly dominated
Zoledronate (i.v.)	£6,854.23	13.34360	£522.75	0.00910	£57,436	£260,018	£393,454	£74,509

*ICER versus next least costly non-dominated strategy

Table 64: Basecase results from 200,000 PSA samples for FRAX risk category 4

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Alendronate	£6,940.02	13.57697	-£3.78	0.00214	-£1,768	£264,599	£400,369	NA
Ibandronate (oral)	£6,940.34	13.57684	-£3.47	0.00201	-£1,726	£264,597	£400,365	Dominated
No treatment	£6,943.81	13.57483	£0.00	0.00000	NA	£264,553	£400,301	Dominated
Risedronate	£6,945.84	13.57692	£2.04	0.00208	£978	£264,593	£400,362	Dominated
Ibandronate (i.v.)	£7,157.83	13.57920	£214.02	0.00437	£49,021	£264,426	£400,218	Extendedly dominated
Zoledronate (i.v.)	£7,474.18	13.58617	£530.37	0.01134	£46,776	£264,249	£400,111	£58,061

*ICER versus next least costly non-dominated strategy

Table 65: Basecase results from 200,000 PSA samples for FRAX risk category 5

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Ibandronate (oral)	£7,466.53	12.32601	-£9.83	0.00183	-£5,379	£239,054	£362,314	NA
Risedronate	£7,471.92	12.32603	-£4.44	0.00184	-£2,406	£239,049	£362,309	£329,090
No treatment	£7,476.36	12.32418	£0.00	0.00000	NA	£239,007	£362,249	Dominated
Alendronate	£7,478.51	12.32595	£2.14	0.00177	£1,213	£239,041	£362,300	Dominated
Ibandronate (i.v.)	£7,671.16	12.32710	£194.80	0.00292	£66,739	£238,871	£362,142	Extendedly dominated
Zoledronate (i.v.)	£8,001.50	12.33301	£525.14	0.00882	£59,513	£238,659	£361,989	£75,873

*ICER versus next least costly non-dominated strategy

Table 66: Basecase results from 200,000 PSA samples for FRAX risk category 6

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£7,616.23	10.59846	£0.00	0.00000	NA	£204,353	£310,338	NA
Alendronate	£7,618.25	10.60009	£2.02	0.00163	£1,242	£204,384	£310,384	£1,242
Risedronate	£7,619.22	10.59995	£3.00	0.00149	£2,008	£204,380	£310,379	Dominated
Ibandronate (oral)	£7,620.80	10.59974	£4.57	0.00128	£3,574	£204,374	£310,371	Dominated
Ibandronate (i.v.)	£7,833.82	10.60192	£217.59	0.00346	£62,921	£204,205	£310,224	Extendedly dominated
Zoledronate (i.v.)	£8,138.66	10.60773	£522.44	0.00927	£56,383	£204,016	£310,093	£68,144

*ICER versus next least costly non-dominated strategy

Table 67: Basecase results from 200,000 PSA samples for FRAX risk category 7

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Alendronate	£7,162.84	9.10272	-£5.67	0.00150	-£3,766	£174,892	£265,919	NA
Risedronate	£7,164.94	9.10275	-£3.57	0.00154	-£2,321	£174,890	£265,918	£64,125
No treatment	£7,168.51	9.10121	£0.00	0.00000	NA	£174,856	£265,868	Dominated
Ibandronate (oral)	£7,177.99	9.10236	£9.48	0.00114	£8,295	£174,869	£265,893	Dominated
Ibandronate (i.v.)	£7,392.35	9.10398	£223.84	0.00276	£80,986	£174,687	£265,727	Extendedly dominated
Zoledronate (i.v.)	£7,702.81	9.10946	£534.31	0.00825	£64,770	£174,486	£265,581	£80,140

*ICER versus next least costly non-dominated strategy

Table 68: Basecase results from 200,000 PSA samples for FRAX risk category 8

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
No treatment	£7,830.38	7.91916	£0.00	0.00000	NA	£150,553	£229,744	NA
Risedronate	£7,833.78	7.92086	£3.40	0.00170	£1,996	£150,583	£229,792	£1,996
Ibandronate (oral)	£7,836.05	7.92098	£5.67	0.00182	£3,112	£150,584	£229,793	£19,441
Alendronate	£7,839.16	7.92096	£8.78	0.00181	£4,864	£150,580	£229,790	Dominated
Ibandronate (i.v.)	£8,049.13	7.92224	£218.75	0.00308	£70,929	£150,396	£229,618	Extendedly dominated
Zoledronate (i.v.)	£8,378.29	7.92722	£547.91	0.00807	£67,934	£150,166	£229,438	£86,829

*ICER versus next least costly non-dominated strategy

Table 69: Basecase results from 200,000 PSA samples for FRAX risk category 9

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Alendronate	£11,167.83	6.90026	-£7.38	0.00232	-£3,175	£126,837	£195,840	NA
No treatment	£11,175.20	6.89794	£0.00	0.00000	NA	£126,784	£195,763	Dominated
Risedronate	£11,176.94	6.90016	£1.74	0.00223	£782	£126,826	£195,828	Dominated
Ibandronate (oral)	£11,195.85	6.89967	£20.65	0.00174	£11,891	£126,798	£195,794	Dominated
Ibandronate (i.v.)	£11,430.76	6.90139	£255.55	0.00345	£73,995	£126,597	£195,611	Extendedly dominated
Zoledronate (i.v.)	£11,734.98	6.90722	£559.78	0.00929	£60,287	£126,409	£195,482	£81,469

*ICER versus next least costly non-dominated strategy

Table 70: Basecase results from 200,000 PSA samples for FRAX risk category 10

	Mean outcomes (discounted)		**Incremental outcomes versus no treatment (discounted)**		**ICER vs. no treatment**	**Net benefit at £20K per QALY**	**Net benefit at £30K per QALY**	**Incremental analysis***
Treatment strategy	Cost	QALYs	Cost	QALYs				
Risedronate	£18,699.06	4.56088	-£27.62	0.00220	-£12,566	£72,519	£118,127	NA
Alendronate	£18,704.64	4.56166	-£22.04	0.00297	-£7,411	£72,529	£118,145	£7,194
Ibandronate (oral)	£18,724.98	4.56022	-£1.70	0.00154	-£1,104	£72,479	£118,082	Dominated
No treatment	£18,726.68	4.55868	£0.00	0.00000	NA	£72,447	£118,034	Dominated
Ibandronate (i.v.)	£18,943.03	4.56193	£216.35	0.00325	£66,600	£72,296	£117,915	Extendedly dominated
Zoledronate (i.v.)	£19,257.85	4.56644	£531.17	0.00775	£68,498	£72,071	£117,735	£115,714

*ICER versus next least costly non-dominated strategy