Pharmacological therapies for the prevention of fractures in men

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TABLE OF CONTENTS

[Intervention Protocol]

Pharmacological therapies for the prevention of fractures in men

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To determine the benefits and harms of bisphosphonates, parathyroid or parathyroid-related protein analogues, denosumab, and romosozumab therapy for the primary and secondary prevention of fractures in men.

BACKGROUND

Description of the condition

Fractures are broken bones. They can be separated into complete fractures (where the affected bone is divided into two or more pieces) or partial (incomplete) fractures, in which the fracture line does not extend through the cortex (outer layer). Trauma is required for a fracture to occur, but low trauma can be sufficient to cause a fracture if bone strength is reduced. One cause of reduced bone strength and consequently an increased risk of fracture is osteoporosis, a skeletal disorder that is characterised by compromised bone mass or quality (or both) (NIH Consensus Statement 2001). Fragility fractures (also called osteoporotic fractures or low-trauma fractures) associated with osteoporosis are defined as fractures that occur after a fall from a standing height or less.

Population-based studies have demonstrated an association between low bone mineral density (BMD) and fracture risk (NIH Consensus Statement 2001). BMD can be measured by dual energy X-ray absorptiometry (DXA), and results are presented as both T-scores and z-scores. The T-score represents the number of standard deviations above or below the sex-matched population mean BMD for young adults, while the z-score is also age-matched. The relative risk of fracture increases with each standard deviation that the T-score decreases, at a similar rate in men and women, but men have a lower absolute fracture risk at any T-score (Cummings 2006). The World Health Organization recommends using the same classification of BMD to define osteoporosis in men and women aged 50 years and older: BMD 2.5 or more standard deviations below the young female reference range (T-score of -2.5 or less) (WHO 2004). In men below 50 years of age, the diagnosis of osteoporosis requires low BMD (z-score of -2 or less) in addition to either a previous fragility fracture or the presence of a risk factor for osteoporosis (e.g. hypogonadism or glucocorticoid therapy) (Lewiecki 2008).

Bone strength depends not only on BMD, but also on other properties such as the bone micro-architecture, its degree of mineralisation, bone geometry and bone turnover (Greenspan 2012; Mosekilde 1988). Bone mass and strength in men is further determined by attaining peak bone mass during growth and subsequent age-related bone loss. Compared with women, men attain greater peak bone mass, and have larger and stronger bones in young adulthood (Lambert 2011). Bone loss commences soon after peak bone mass is achieved (Nordström 2007), with longitudinal studies suggesting that the rate of loss increases after the age of 70 years in men (Berger 2008), and less rapidly than in women. In men, the outer cortical layer of bone surface area remains relatively stable (Lambert 2011), while the inner trabecular portion becomes thinner with age (Khosla 2006). However, the majority of non-vertebral fractures occur in men who do not meet the BMD criteria for osteoporosis (Seeman 2006).

Hip fractures are the main reason for fracture-related mortality. The incidence rate of hip fracture in men is reported to be three per 1000 person-years (e.g. following 100 men for 10 years equals 1000 person-years), compared to seven per 1000 person-years in women (Trajanoska 2018). Data from a large cohort (>480,000 individuals) in Minnesota in the USA showed a decline in the incidence of hip fractures in women from 1989 to 1991 and 2009 to 2011, but no decline was observed in men (Amin 2014). Significantly, hip fractures are associated with greater mortality in men than in women, with a mortality rate of up to 37.5% within a year of fracture (Center 1999; Orwoll 1995). This is partly due to men being older, and having more comorbidities, at the time of fracture (Trombetti 2002). An estimated nine million osteoporotic-related fractures occur annually worldwide, and 39% occur in men (Johnell 2006). Men are offered anti-resorptive treatment (treatment that blocks the breakdown of bone) less frequently than women (4.5% verus 49.5%), and are given any kind of treatment against osteoporosis less frequently than women (27% versus 71%) (Kiebzak 2002).

Treatment for the prevention of fractures in patients with osteoporosis is targeted at reducing the incidence of fragility fractures and improving BMD. Non-pharmacological interventions include weight-bearing exercise (which addresses risk factors for falls, such as poor balance); smoking cessation; and avoiding excessive alcohol intake (Black 2016). Calcium and vitamin D supplementation are used in those who are deficient (Black 2016; Eastell 1998). Strontium ranelate has previously been suggested as appropriate for use in men (Kaufman 2013), but the European Medicines Agency (EMA) advises against this (EMA 2013); and the manufacturer discontinued marketing and distributing strontium ranelate in 2017 due to restricted indication/limited use and a decrease of patients treated (Servier 2017). Calcitonin has been shown to be effective against osteoporosis in women (Chesnut 2000), but is usually not recommended due to low efficacy and concern about cancer side-effects (of various types, including basal cell carcinoma) (EMA 2012). Testosterone replacement in hypogonadal men (i.e. men with diminished testes function) has also been shown to be effective at increasing BMD (Katznelson 1996), but no evidence exists regarding fracture risk (Tracz 2006; Yeap 2018). The role of testosterone therapy in eugonadal men (i.e. men with normal testes function) remains controversial (Katznelson 1996).

Description of the intervention

Pharmacologic interventions for the prevention of fragility fractures include bisphosphonates which block the breakdown of bone (anti-resoprtive) and are considered to be first-line; and anabolic therapies including parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) analogues which build bone, monoclonal antibodies including denosumab (which has anti-resorptive properties), and romosozumab (a sclerostin inhibitor that has anabolic actions), all of which are considered to be second-line options.

Bisphosphonates may be administered either orally (such as alendronate, risedronate, ibandronate, and etidronate) or via intravenous infusion (ibandronate, pamidronate and zoledronic acid). Bisphosphonates improve BMD and reduce fracture risk in postmenopausal women (Barrionuevo 2019; Black 2007; Wells 2008a; Wells 2008b). Several systematic reviews have considered the effect of bisphosphonates in men (Nayak 2017; Chen 2015; Zhou 2016; Shi 2019). Most of them have reported a significant reduction in vertebral and non-vertebral fractures, but they were limited by a small number of included studies and underpowered analyses.

Bisphosponate therapy is generally well tolerated. The most common side effects associated with oral use are gastrointestinal (Wells 2008a; Wells 2008b). An acute-phase 'flu-like' illness is the most common adverse event after intravenous (but not oral)

bisphosphonate (Black 2007). Other adverse effects after both intravenous and oral use include transient hypocalcaemia and severe musculoskeletal pain, and worsening renal function has also been reported. Rare, but important, adverse effects include osteonecrosis of the jaw and atypical femoral fractures. Whereas most cases of atypical femoral fracture have been reported in younger women receiving long-term bisphosphonate therapy (Shane 2010), there does not appear any gender predilection for the development of osteonecrosis of the jaw. There have been case reports of oesophageal cancer with bisphosphonate use, but the risk reported in cohort studies is inconclusive (Cardwell 2010; Green 2010; Vinogradova 2013). People with erosive oesophagitis had crystalline deposits similar to bisphosphonate in oesophagus biopsies, suggesting there could be a link between bisphosphonate and inflammation of the oesophagus (Abraham 1999). There might be an increased risk of atrial fibrillation from zoledronic acid (Black 2007), and possibly a small increased risk of atrial fibrillation from oral bisphophonates (FDA 2007).

Teriparatide (a parathyroid hormone (PTH) analogue) and abaloparatide (a PTH-related protein analogue) reduce the risk of fracture in postmenopausal osteoporotic women (Lindsay 1997; Neer 2001; Reginster 2019). They are administered by subcutaneous injection (into the tissue under the skin). There is limited evidence on the effect of PTH or PTH-related protein analogues in men. One placebo-controlled trial assessed teriparatide in men with osteoporosis, but there was a limited assessment of fracture risk as the trial stopped early (Orwoll 2003). A follow-up study of the same trial found that teraparatide reduced the risk of vertebral fracture by 51%, but this analysis was underpowered and the between-group difference with placebo was not statistically significant (Kaufman 2005).

Teriparatide and abaloparatide seem to be generally well tolerated (Black 2003; Finkelstein 2003; Hodsman 2003), but there is limited evidence of safety in men, particularly for abaloparatide (Reginster 2019). Common adverse events include hypercalcaemia (high calcium levels in blood) and hypercalcuria (high calcium levels in urine). There are also reports of osteosarcoma, but the incidence seems to be low (three reports in more than one million patients treated with teriparatide) and the link is unproven in humans (Cipriani 2012).

Denosumab, which is administered subcutaneously, increases BMD and reduces the risk of fractures in postmenopausal women with osteoporosis (Beaudoin 2016). Most trials of denosumab in men have been performed in the setting of androgen deprivation therapy in patients with non-metastatic prostate cancer, in which it reduces fracture risk (Smith 2009). There are few trials that have tested denosumab in men unrelated to this setting, and these trials have only assessed outcomes relating to BMD, not fractures (Orwoll 2012). Denosumab appears to be well tolerated (Bone 2008; Brown 2009; Cummings 2009; Khosla 2009; Lewiecki 2007; McClung 2006); and in women, the risk of adverse events is likely to be similar to bisphosphonates (Beaudoin 2016). Possible serious adverse events of denosumab include hypocalcaemia, atypical femur fractures, osteonecrosis of the jaw and infections. The long-term safety of denosumab is uncertain (Sun 2013).

A systematic review that included trials in both men and women with osteoporosis found that romosozumab (subcutaneous administration) is effective in reducing fractures and has a safety profile similar to other treatment options (Mariscal 2020). However, only approximately 18 out of 5974 trial participants were male (the exact numbers are not possible to extract from the paper), there were no trials with long-term follow-up (i.e. more than 12 months), and the systematic review was unable to draw a conclusion about risk of cardiovascular adverse events. Romosozumab is currently only approved by the Food and Drug Administration (FDA) for the treatment of women with osteoporosis, apparently due to uncertainties about the risk of cardiac events (FDA 2019).

How the intervention might work

Bone remodelling is a lifelong process that allows the renewal of bone and maintenance of bone health through the replacement of old bone with new bone. Osteoclasts are cells that are responsible for bone resorption, whilst bone formation is reliant on the actions of osteoblasts (Manolagas 2000). The balance between osteoclast and osteoblast activity determines net gain or loss of bone (Manolagas 2000).

Bisphosphonates bind avidly to hydroxyapatite (the collagen matrix that is responsible for bone mineralisation and strength), and are subsequently internalised by osteoclasts. This reduces the activity of osteoclasts, and contributes to the death of these cells, ultimately resulting in reduced activation frequency of the bone multicellular unit, reduced osteoclastic bone resorption, and a net gain of bone.

Parathyroid hormone and parathyroid hormone-related protein (PTHrP) stimulate osteoclast function and bone formation (Rosen 2001). Denosumab is a monoclonal antibody that binds to nuclear factor-kappa ligands (RANKL) which results in reduced formation and function of osteoclasts. Romosozumab both increases bone formation and reduces resorption by inhibiting a regulatory factor (sclerostin) of bone growth (Bandeira 2017).

Why it is important to do this review

The benefits and harms of pharmacological therapy for the prevention of fractures in men with osteoporosis are uncertain. Previous reviews on bisphosphonates included few trials (Chen 2015; Nayak 2017; Xu 2017), could not exclude biases (Chen 2015), did not report separate results for men (Shi 2019), or reported insignificant effects (Zhou 2016). Furthermore, there was uncertainty abut whether the risk of non-vertebral fractures was reduced, due to imprecision in the effect estimates as numbers of participants were small (Nayak 2017; Xu 2017; Zhou 2016). There was also incomplete reporting of harms in previous reviews and few trials only included men (Chen 2015; Nayak 2017; Shi 2019; Xu 2017; Zhou 2016).

Previous reviews of PTH/PTHrP analogues (Lindsay 1997; Neer 2001; Reginster 2019), denosumab (Beaudoin 2016), and romosozumab (Mariscal 2020) have mainly focused on effectiveness and safety in women. There are trials of PTH/PTHrP analogues (Langdahl 2009; Orwoll 2003), denosumab (Nakamura 2014; Orwoll 2012; Smith 2009) and romosozumab (Lewiecki 2018) that report results for men only, but no systematic reviews have yet synthesised these data.

As explained above, there are significant epidemiological and physiological differences between men and postmenopausal women with respect to factors such as fracture risks, causes of osteoporosis, and age-related changes in BMD. Therefore, although there is evidence of anti-fracture efficacy of osteoporosis treatment

options in postmenopausal women (Barrionuevo 2019; Beaudoin 2016; Black 2007; Lindsay 1997; Mariscal 2020; Neer 2001; Reginster 2019; Wells 2008a; Wells 2008b), it is important to establish the efficacy and safety of fracture prevention in men. A synthesis of the available literature is therefore now warranted. The EMA's Committee for Medicinal Products for Human Use (CHMP 2006) consider there is no rationale for making a clear distinction between prevention and treatment of fragility fractures (CHMP 2006). WHO also considers fracture probabilities based on BMD and other clinical information is more clinically useful than reliance on BMD alone (WHO 2004). Accordingly, this review will assess the efficacy of fracture prevention in men with and without a prior history of fragility fractures. It will be conducted according to the guidelines recommended by the Cochrane Musculoskeletal Editorial Board (Ghogomu 2014).

OBJECTIVES

To determine the benefits and harms of bisphosphonates, parathyroid or parathyroid-related protein analogues, denosumab, and romosozumab therapy for the primary and secondary prevention of fractures in men.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) in this review. We will include studies reported as full text. Studies published as abstracts and unpublished data will be categorised as awaiting assessment; their data will be included in updates of this review (provided the data are published). For trials that included data for both men and women combined, we will attempt to contact trialists and request data for men separately. Unpublished data on adverse events will be included. There will be no language restrictions. We will exclude cross-over randomised trials, given the long half-life (over 10 years for bisphosphonates) and duration of effect (up to 12 months for denosumab and romosozumab).

Types of participants

We will include trials that include men aged 50 years or older with or without previous fragility fractures. Trials that include a mix of men and women will be included, provided that data are reported separately for men. We will exclude trials that include men with osteoporosis secondary to underlying disease or medication.

Types of interventions

We will include trials comparing bisphosphonates, PTH or PTHrP analogues, denosumab, or romozosumab (alone or with calcium or vitamin D, or both) with either placebo or an active comparator. Bisphosphonates could be administered orally (e.g. alendronate, risedronate, etidronate, ibandronate) or intravenously (e.g. pamidronate, ibandronate, zoledronic acid). The PTH and PTHrP analogues (teriparatide and abaloparatide), denosumab, and romosozumab are all administered by subcutaneous injections (daily, once every six months, and monthly, respectively).

Comparators may include the following.

1. Placebo.
2. Any of the interventions listed above, i.e. another active intervention.
3. Other established pharmacological treatments for fracture prevention, including calcitonin and testosterone therapy, as well as calcium and vitamin D supplementation.
4. Non-pharmacological therapies (diet, exercise, smoking cessation, mechanical stimulation from vibration).

Types of outcome measures

Major outcomes

1. Incident hip fractures
2. Incident symptomatic vertebral fractures
3. Incident other (not hip or vertebral) fractures (e.g. wrist, humeral head, etc.)
4. Disability, as measured by osteoporosis-specific measures (eg. Osteoporosis Functional Disability Questionnaire) or generic measures (e.g. the 36-Item Short Form Survey (SF-36) physical function component)
5. Total number of adverse events
6. Number of study withdrawals due to adverse events
7. Number of serious adverse events

Minor outcomes

1. Radiographic (asymptomatic) vertebral fractures. Although there is no widely accepted definition or cut-off values for radiographic vertebral fractures that are based on clinically meaningful outcomes, we will extract these data including the definitions used in individual trials.
2. Pain intensity (e.g. Visual Analogue Scale (VAS))
3. Quality of life, as assessed by osteoporosis-specific measures (e.g. Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) or generic measures (e.g. SF-36 mental health component))

Timing of outcome assessments

We will assess outcomes according to the following time frames: between six months and one year; greater than one year to two years; and then yearly thereafter, if data are available. The final time point reported in the trials will be our primary time point. If outcomes are recorded at multiple time points, we will collect the last measure within each of our pre-defined time frames.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase via Ovid. For assessments of adverse effects, we will search the websites of the regulatory agencies FDA-MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm), European Medicines Evaluation Agency (http://www.ema.europa.eu), Australian Adverse Drug Reactions Bulletin (https://www.tga.gov.au/publication/australian-adverse-drug-reactions-bulletin), and UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmacovigilance and drug safety updates (http://www.mhra.gov.uk).

We will also conduct a search of ClinicalTrials.gov and the WHO trials portal. We will search all databases from their inception to

the present, and we will impose no restriction on language of publication. See Appendix 1 for the MEDLINE search strategy.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review. We will search regulatory agency sources including Drugs@FDA, OpenTrialsFDA, Therapeutic Goods Administration (TGA) and EU Clinical Trials Register (EUCTR).

Data collection and analysis

Selection of studies

Two review authors (CS, LCB) will independently screen titles and abstracts of all the potentially relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publications and two review authors (SS, LCB) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (RJ). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (PRISMA Group 2009) and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot on at least one study in the review. One review author (LCB) will extract study characteristics from included studies. A second review author (RJ or RB) will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, trial registration or study protocol if available, and date of study.
2. Participants: number (N), mean age, age range, demographics, ethnicity/race, diagnostic criteria of symptomatic and radiographic vertebral fracture (and osteoporosis if different from WHO criteria), baseline BMD data, prior fracture, comorbidities, inclusion criteria, exclusion criteria, treatment regimen and duration, outcomes and timing of outcome assessment.
3. Interventions: intervention regimen, including dose and duration of treatment, mode of delivery.
4. Comparison regimen, including dose and duration of treatment, mode of delivery; concomitant medications, co-interventions and excluded medications.
5. Outcomes: primary and secondary outcomes specified and collected, and time points reported (regardless of whether analysed in this review).
6. Characteristics of the design of the trial, as outlined below in Assessment of risk of bias in included studies.
7. Notes: funding for the trial, and notable declarations of interest of trial authors.

Two review authors (CS, LCB) will independently extract outcome data from included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way and when data were transformed or estimated from a graph. We will resolve disagreements by consensus or by involving a third person (RJ). One review author (LCB) will transfer data into the Review Manager (RevMan 2020) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

We will use software such as PlotDigitizer (PlotDigitizer 2015), to extract data from graphs or figures. These data will also be extracted in duplicate. If multiple measures for quality of life are reported, we will prioritise data from osteoporosis-specific measures (e.g. QUALEFFO).

If final values, values adjusted for baseline, and change-from-baseline values are reported for the same outcome in the same trial, we will extract values adjusted for baseline over final values over change-from-baseline. If data are analysed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as-treated), we will extract ITT preferentially.

Main planned comparisons

1. Any bisphosphonate (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both)

2. Any PTH/PTHrP analogue (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both)

3. Denosumab (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both)

4. Romosozumab (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both)

Other planned analyses

5. Any pharmacological intervention (i.e. bisphosphonate, PTH/PTHrP analogue, denosumab or romosozumab; alone or with calcium or vitamin D, or both) versus non-pharmacological therapy (alone or with calcium or vitamin D, or both)

6. Any pharmacological intervention (i.e. bisphosphonate, PTH/PTHrP analogue, denosumab or romosozumab; alone or with calcium or vitamin D, or both) versus any other established pharmacological class of therapy (alone or with calcium or vitamin D, or both)

7. Any bisphosphonate (alone or with calcium or vitamin D, or both) versus any other bisphosphonate (alone or with calcium or vitamin D, or both)

Assessment of risk of bias in included studies

Two review authors (LCB, RJ) will independently assess risk of bias for each study using version 2 of the Cochrane 'Risk of bias' tool for randomised trials (RoB 2) (Higgins 2021). We will assess risk of bias for the effect of assignment to the intervention (e.g. the intention-to-treat effect) for each time point of each outcome measure. We will resolve any disagreements by discussion or by involving another author (RB). We will assess the risk of bias according to the following domains.

1. Bias arising from the randomisation process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

To address these types of bias we will use the signalling questions recommended in RoB 2. We will assign one of the following judgements for each potential source of bias: high risk of bias, some concerns, or low risk of bias. We will provide a quote from the study report, together with a justification for our judgement, in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Subsequently, we will derive a 'Risk of bias' rating for each pre-specified outcome in each study, in accordance with the following suggestions.

1. Low risk of bias: the trial is judged to be at low risk of bias for all domains.
2. Some concerns: the trial is judged to raise some concerns for at least one domain, but not to be at high risk of bias for any domain.
3. High risk of bias: the trial is judged to be at high risk of bias for at least one domain, or the trial is judged to have some concerns for multiple domains, in a way that substantially lowers confidence in the results.

We will consider blinding separately for different key outcomes. Self-reported outcomes and assessor-reported outcomes will be judged separately. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will consider the impact of missing data by key outcomes.

We will use the 'RoB Excel' tool (available at riskofbias.info) for ‘risk of bias’ assessments and will present the figures generated by the 'Risk of bias' tool to provide summary assessments of the risk of bias. For cluster-RCTs, we will add an additional domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation, as recommended in the RoB 2 guidance for cluster-randomised trials.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios or Peto odds ratios when the outcome is a rare event (approximately less than 10%), and we will use 95% confidence intervals (CIs). Continuous data will be analysed as mean difference (MD) or standardised mean difference (SMD), depending on whether the same scale is used to measure an outcome, along with 95% CIs. We will enter data presented as a scale with a consistent direction of effect across studies.

When different scales are used to measure the same conceptual outcome (e.g. disability), SMDs will be calculated instead, with corresponding 95% CIs. SMDs will be back-translated to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial) (Higgins 2021a).

For dichotomous outcomes, the number needed-to-treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) will be calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator (Cates 2008). The NNTB or NNTH for continuous measures will be calculated using the Wells calculator (available at the Cochrane Musculoskeletal Editorial office, musculoskeletal.cochrane.org/). The minimal clinically important difference will be used in the calculation of NNTB or NNTH: 10 points on a 100-point scale, or 10% for function or disability or quality-of-life, for input into the calculator.

For dichotomous outcomes, the absolute per cent change will be calculated from the difference in the risks between the intervention and control group using GRADEpro GDT (GRADEpro GDT 2015) and expressed as a percentage. The relative per cent change will be calculated as the risk ratio - 1, and expressed as a percentage.

For continuous outcomes, we will calculate the absolute per cent change by dividing the mean difference by the scale of the measure, and express this as a percentage. The relative difference will be calculated as the absolute benefit (mean difference) divided by the baseline mean of the control group, and expressed as a percentage.

In the 'Effects of interventions' section and the 'What happens' column of the 'Summary of findings' table, we will provide the absolute per cent change, the relative per cent change from baseline, and the NNTB or NNTH (the NNTB or NNTH will be provided only when the outcome shows a clinically significant difference).

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. bisphosphonate A versus placebo and bisphosphonate B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

If we identify any cluster-RCTs or studies that included more than one joint in the analysis, we will multiply the standard error of the effect estimate (from an analysis ignoring clustering) by the square root of the design effect (inflated variances), according to the methods described in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b). The meta-analysis using the inflated variances will be performed using the generic inverse-variance approach.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only or when data are not available for all participants). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. Any assumptions and imputations to handle missing data will be clearly described and the effect of imputation will be explored by sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), the withdrawal rate will be calculated using the number of patients randomised in the group as the denominator. For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD based on the number of participants analysed at that time point. If the number of participants analysed is not presented for each time point, the number randomised in each group at baseline will be used.

Where possible, missing standard deviations will be computed from other statistics such as standard errors, CIs or P values, according to the methods recommended in the *Cochrane Handbook* (Deeks 2021). If standard deviations cannot be calculated, they will be imputed (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

Clinical and methodological diversity will be assessed in terms of participants, interventions, outcomes and study characteristics of the included studies to determine whether a meta-analysis is appropriate (Data extraction and management). We will do this by observing these data from the data extraction tables. Statistical heterogeneity will be assessed by visual inspection of the forest plots to assess for obvious differences in results between the studies, and using the I^2 and Chi^2 statistical tests.

As recommended in the *Cochrane Handbook* (Deeks 2021), the interpretation of an I^2 value of 0% to 40% might not be important; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity. As noted in the *Cochrane Handbook* (Deeks 2021), we will keep in mind that the importance of I^2 depends on the magnitude and direction of effects and the strength of evidence for heterogeneity.

The Chi^2 test will be interpreted where a P value of 0.10 or less indicates evidence of statistical heterogeneity. If we identify substantial heterogeneity we will report it and investigate possible causes by following the recommendations in section 10.11 of the *Cochrane Handbook*.

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small-study biases. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry as outlined in chapter 13 of the Cochrane
Handbook for Systematic Reviews of Interventions (Page 2021) and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, and will follow the recommendations in chapter 13 of the *Cochrane Handbook* (Page 2021).

We will compare the fixed-effects estimate against the random-effects model to assess the possible presence of small-sample bias in the published literature (i.e. in which the intervention effect is more beneficial in smaller studies). In the presence of small-sample bias, the random-effects estimate of the intervention is more beneficial than the fixed-effect estimate (Page 2021).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the WHO for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We plan to pool outcomes from trials with similar characteristics (participants, interventions and common comparators, outcome measures and timing of outcome measurement) to provide estimates of benefit and harm. We plan to synthesise effect estimates using a random-effects meta-analysis model based on the assumption that clinical diversity is likely to exist, and that different studies are estimating different intervention effects.

Where we cannot pool data, we plan to present effect estimates and 95% CIs of each trial in tables, and summarise the results in text. We plan to examine the overall effect of bisphosphonates as the primary analysis and stratify by individual bisphosphonates: alendronate, risedronate, pamidronate, ibandronate, clodronate and zoledronic acid. The primary analysis will include all included trials, irrespective of their judged risk of potential bias.

Subgroup analysis and investigation of heterogeneity

We plan to carry out subgroup analyses for the following factors.

1. Absence versus presence of prior fragility fracture, i.e. primary compared with secondary prevention of fractures. Prior fragility fracture confers higher absolute fracture risk. The anti-fracture efficacy of osteoporosis treatment in primary and secondary prevention settings may differ.
2. Age. We will assess anti-fracture efficacy in patients above versus below 75 years of age. A meta-analysis of post-menopausal women questioned the anti-fracture efficacy in the elderly (Järvinen 2015).
3. Time. We will assess anti-fracture efficacy at one versus two versus three versus more than three years' follow-up. Short follow-up time might not be sufficient to detect anti-fracture efficacy in terms of absolute risk reduction.

We will use the following outcomes in subgroup analyses.

1. Incident hip fractures.
2. Incident symptomatic vertebral fractures.
3. Incident other (not hip or vertebral) fractures (e.g. wrist, humeral head etc.).

We will use the formal test for subgroup interactions in Review Manager 5.4 (RevMan 2020) and will use caution in the interpretation of subgroup analyses, as advised in chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2021).

Sensitivity analysis

We plan to carry out the following sensitivity analyses to investigate the robustness of the treatment effect on incident hip fractures, incident symptomatic vertebral fractures, and incident other fractures.

1. Selection bias: we will remove the trials that reported inadequate or unclear allocation concealment from the meta-analysis to see if this changes the overall treatment effect.
2. Detection bias: we will remove the trials that reported inadequate or unclear patient or assessor blinding from the meta-analysis to see if this changes the overall treatment effect.
3. Overall bias: we will remove the outcomes with some concerns or high risk of bias to see if this changes the overall treatment effect.

Interpreting results and reaching conclusions

We will follow the guidelines in Chapter 15 of the *Cochrane Handbook* (Schünemann 2021) for interpreting results, and will be aware of distinguishing a lack of evidence of effect from a lack of effect. We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and will suggest priorities for future research and outline what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the following outcomes.

1. Incident hip fractures.
2. Incident symptomatic vertebral fractures.
3. Incident other (not hip or vertebral) fractures (e.g. wrist, humeral head, etc.).
4. Total number of adverse events.
5. Number of study withdrawals due to adverse events.
6. Number of serious adverse events.
7. Disability as measured by osteoporosis-specific or generic measures.

The comparisons in the 'Summary of findings' tables will be as follows. We are unlikely to provide a 'Summary of findings' table for every possible comparison identified, but will address the most relevant comparisons to inform current management.

1. Any bisphosphonate (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both).
2. Any PTH/PTHrP analogue (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both).
3. Denosumab (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both).
4. Romosozumab (alone or with calcium or vitamin D, or both) versus placebo (alone or with calcium or vitamin D, or both).

Two people (LCB, RJ) will independently assess the certainty of the evidence. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes and use the overall RoB 2 judgement in the GRADE assessments. We will use the following criteria to describe the confidence in the evidence.

1. High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
3. Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
4. Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We will decrease the GRADE rating by one, two, or three levels, up to a maximum of three levels (i.e. a judgement of very low quality) for any criteria, based on the level of concern it raises. We will use GRADEpro software to prepare the 'Summary of findings' tables (GRADEpro GDT 2015). We will use version 3 of the GRADEpro view to display the tables. We will justify all decisions to downgrade the certainty of evidence for each outcome using footnotes and we will make comments to aid the reader's understanding of the review where necessary. We will provide the NNTB or NNTH, absolute and relative per cent change in the 'What happens' column of the 'Summary of findings' tables, as described above, with the exception of the absolute difference for dichotomous outcomes which is displayed by default in version 3 of the GRADEpro view.

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REFERENCES

Additional references

Abraham 1999

Abraham SC, Cruz-Correa M, Lee LA, et al. Alendronate-associated esophageal injury: pathologic and endoscopic features. *Modern Pathology* 1999;**12**:1152.

Amin 2014

Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton III LJ. Trends in fracture incidence: a population-based study over 20 years. *Journal of Bone and Mineral Research* 2014;**29**:581-9.

Bandeira 2017

Bandeira L, Lewiecki EM, Bilezikian JP. Romosozumab for the treatment of osteoporosis. *Expert Opinion on Biological Therapy* 2017;**17**(2):255-63.

Barrionuevo 2019

Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2019;**104**:1623.

Beaudoin 2016

Beaudoin C, Jean S, Bessette L, Ste-Marie LG, Moore L, Brown JP. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. *Osteoporosis International* 2016;**27**(9):2835-44.

Berger 2008

Berger C, Langsetmo L, Joseph L, Hanley DA, Davison KS, Josse R, et al. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. *Canadian Medical Association Journal* 2008;**178**(13):1660-8.

Black 2003

Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *New England Journal of Medicine* 2003;**349**(13):1207-15.

Black 2007

Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *New England Journal of Medicine* 2007;**356**(18):1809-22.

Black 2016

Black DM, Rosen CJ. Postmenopausal osteoporosis. *New England Journal of Medicine* 2016;**374**(3):254-62.

Bone 2008

Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *Journal of Clinical Endocrinology and Metabolism* 2008;**93**:2149.

Brown 2009

Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, De Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *Journal of Bone and Mineral Research* 2009;**24**:153.

Cardwell 2010

Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. *JAMA* 2010;**304**:657.

Cates 2008 [Computer program]

Visual Rx. Version 3. Available at www.nntonline.net, 2008.

Center 1999

Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *The Lancet* 1999;**353**:878.

Chen 2015

Chen L, Wang G, Zheng F, Zhao H, Li H. Efficacy of bisphosphonates against osteoporosis in adult men: a meta-analysis of randomized controlled trials. *Osteoporosis International* 2015;**26**(9):2355-63.

Chesnut 2000

Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *American Journal of Medicine* 2000;**109**(4):267.

CHMP 2006

European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis Revision 2. https://www.ema.europa.eu/en/evaluation-new-medicinal-products-treatment-primary-osteoporosis 16 November 2006.

Cipriani 2012

Cipriani C, Irani D, Bilezikian JP. Safety of osteoanabolic therapy: a decade of experience. *Journal of Bone and Mineral Research* 2012;**27**:2419.

Cummings 2006

Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. *Journal of Bone and Mineral Research* 2006;**21**(10):1550-6.

Cummings 2009

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *New England Journal of Medicine* 2009;**361**:756.

Deeks 2021

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Eastell 1998

Eastell R. Treatment of postmenopausal osteoporosis. *New England Journal of Medicine* 1998;**338**(11):736.

EMA 2012

European Medicines Agency. European Medicines Agency recommends limiting long-term use of calcitonin medicines. https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-limiting-long-term-use-calcitonin-medicines (accessed 11 August 2021).

EMA 2013

European Medicines Agency. Recommendation to restrict the use of Protelos / Osseor (strontium ranelate). https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-protelososseor-remain-available-further-restrictions (accessed 11 August 2021).

FDA 2007

US Food and Drug Administration. Update of Safety Review Follow-up to the October 1, 2007 Early Communication about the Ongoing Safety Review of Bisphosphonates. www.biospace.com/article/around-the-web/update-of-safety-review-follow-up-to-the-october-1-2007-early-communication-about-the-ongoing-safety-review-of-bisphosphonates-/ (accessed 12 November 2008).

FDA 2019

US Food and Drug Administration. Background information for Bone, Reproductive and Urologic Drugs Advisory Committee 16 January 2019 Biologics license application for romosozumab. www.fda.gov/media/121255/download (accessed 16 January 2019).

Finkelstein 2003

Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *New England Journal of Medicine* 2003;**349**(13):1216-26.

Ghogomu 2014

Ghogomu EA, Maxwell LJ, Buchbinder R, Rader T, Pardo Pardo J, Johnston RV, et al. Updated method guidelines for Cochrane musculoskeletal group systematic reviews and metaanalyses. *Journal of Rheumatology* 2014;**41**(2):194-205.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime, Inc.). Available from www.gradepro.org GRADEpro Guideline Development Tool. McMaster University (developed by Evidence Prime, Inc.). Available from www.gradepro.org, 2015.

Green 2010

Green J, Czanner G, Reeves G, et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. *BMJ* 2010;**341**:c4444.

Greenspan 2012

Greenspan SL, Wagner J, Nelson JB, Perera S, Britton C, Resnick NM. Vertebral fractures and trabecular microstructure in men with prostate cancer on androgen deprivation therapy. *Journal of Bone and Mineral Research* 2013;**28**(2):325-32.

Higgins 2021

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Higgins 2021a

Higgins JPT, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Higgins 2021b

Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Hodsman 2003

Hodsman AB, Hanley DA, Ettinger MP, Bolognese MA, Fox J, Metcalfe AJ, et al. Efficacy and safety of human parathyroid hormone-(1–84) in increasing bone mineral density in postmenopausal osteoporosis. *The Journal of Clinical Endocrinology & Metabolism* 2003;**88**(11):5212-20.

Järvinen 2015

Järvinen TL, Michaëlsson K, Jokihaara J, Collins GS, Perry TL, Mintzes B, et al. Overdiagnosis of bone fragility in the quest to prevent hip fracture. *BMJ* 2015;**350**:h2088.

Johnell 2006

Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos International* 2006;**17**:1726.

Katznelson 1996

Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *The Journal of Clinical Endocrinology & Metabolism* 1996;**81**(12):4358-65.

Kaufman 2005

Kaufman J-M, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky G, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporosis International* 2005;**16**(5):510-6.

Kaufman 2013

Kaufman J-M, Audran M, Bianchi G, Braga V, Diaz-Curiel M, Francis RM, et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. *The Journal of Clinical Endocrinology & Metabolism* 2013;**98**(2):592-601.

Khosla 2006

Khosla S, Riggs BL, Atkinson EJ, Oberg AL, McDaniel LJ, Holets M, et al. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. *Journal of Bone and Mineral Research* 2006;**21**(1):124-31.

Khosla 2009

Khosla S. Increasing options for the treatment of osteoporosis. *New England Journal of Medicine* 2009;**361**:818.

Kiebzak 2002

Kiebzak GM, Beinart GA, Perser K, Ambrose CG, Siff SJ, Heggeness MH. Undertreatment of osteoporosis in men with hip fracture. *Archives of Internal Medicine* 2002;**162**:2217.

Lambert 2011

Lambert JK, Zaidi M, Mechanick JI. Male osteoporosis: epidemiology and the pathogenesis of aging bones. *Current Osteoporosis Reports* 2011;**9**(4):229.

Langdahl 2009

Langdahl BL, Marin F, Shane E, Dobnig H, Zanchetta JR, Maricic M, et al. Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. *Osteoporosis International* 2009;**20**:2095–104.

Lewiecki 2007

Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *Journal of Bone and Mineral Research* 2007;**22**:1832.

Lewiecki 2008

Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi M-L, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. *Bone* 2008;**43**(6):1115-21.

Lewiecki 2018

Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *The Journal of Clinical Endocrinology & Metabolism* 2018;**103**(9):3183-93.

Lindsay 1997

Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *The Lancet* 1997;**350**(9077):550.

Manolagas 2000

Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and impliactions for the pathogenesis and treatment of osteoporosis. *Endocrine Reviews* 2000;**21**:115.

Mariscal 2020

Mariscal G, Nuñez JH, Bhatia S, Barrios C, Domenech-Fernández P. Safety of romosozumab in osteoporotic men and postmenopausal women: a meta-analysis and systematic review. *Monoclonal Antibodies in Immunodiagnosis and Immunotherapy* 2020;**39**(2):29-36.

McClung 2006

McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *New England Journal of Medicine* 2006;**354**:821.

Mosekilde 1988

Mosekilde L. Age-related changes in vertebral trabecular bone architecture—assessed by a new method. *Bone* 1988;**9**(4):247-50.

Nakamura 2014

Nakamura T, Matsumoto T, Sugimoto T, Hosoi T, Miki T, Gorai I, et al. Fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). *The Journal of Clinical Endocrinology & Metabolism* 2014;**99**(7):2599-607.

Nayak 2017

Nayak S, Greenspan SL. Osteoporosis treatment efficacy for men: a systematic review and meta-analysis. *Journal of the American Geriatrics Society* 2017;**65**:490.

Neer 2001

Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New England Journal of Medicine* 2001;**344**(19):1434.

NIH Consensus Statement 2001

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *Journal of the American Medical*

Association 2001 Feb 14;**285**(6):785–95. [DOI: 10.1001/jama.285.6.785]

Nordström 2007

Nordström P, Neovius M, Nordström A. Early and rapid bone mineral density loss of the proximal femur in men. *The Journal of Clinical Endocrinology & Metabolism* 2007;**92**(5):1902-8.

Orwoll 1995

Orwoll ES, Klein RF. Osteoporosis in men. *Endocrine Reviews* 1995;**16**(1):87-116.

Orwoll 2003

Orwoll E, Scheele W, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. *Journal of Bone and Mineral Research* 2003;**18**(1):9-17.

Orwoll 2012

Orwoll E, Teglbjærg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. *The Journal of Clinical Endocrinology & Metabolism* 2012;**97**(9):3161-9.

Page 2021

Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

PlotDigitizer 2015 [Computer program]

Plotdigitizer v2.6.8. Plot Digitizer, 2015. Available at plotdigitizer.sourceforge.net.

PRISMA Group 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *BMJ* 2009;**339**:b2535. [DOI: 10.1136/bmj.b2535]

Reginster 2019

Reginster J, Bianic F, Campbell R, Martin M, Williams SA, Fitzpatrick LA. Abaloparatide for risk reduction of nonvertebral and vertebral fractures in postmenopausal women with osteoporosis: a network meta-analysis. *Osteoporosis International* 2019;**30**(7):1465.

RevMan 2020 [Computer program]

The Cochrane Collaboration The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: The Cochrane Collaboration, 2020.

Rosen 2001

Rosen CJ, Bilezikian JP. Anabolic therapy for osteoporosis. *The Journal of Clinical Endocrinology & Metabolism* 2001;**86**(3):957-64.

Schünemann 2021

Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, Akl EA, Guyatt GH. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Seeman 2006

Seeman E, Bianchi G, Khosla S, Kanis J, Orwoll E. Bone fragility in men-where are we? *Osteoporosis International* 2006;**17**(11):1577-83.

Servier 2017

Servier. Cessation of marketing of Protelos/Osseor: Extract of the letter sent to European Medicine Agency (EMA) and national European Agencies on 10 February 2017. servier.com/en/news/cessation-of-marketing-of-protelososseor-extract-of-the-letter-sent-to-european-medicine-agency-ema-and-national-european-agencies-on-10-february-2017/ (accessed 14 March 2017).

Shane 2010

Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research* 2010;**25**(11):2267-94.

Shi 2019

Shi L, Min N, Wang F, Xue QY. Bisphosphonates for secondary prevention of osteoporotic fractures: a Bayesian network meta-analysis of randomized controlled trials. *BioMed Research International* 2019;**2019**:10.

Smith 2009

Smith MR, Egerdie B, Toriz NH, Feldman R, Tammela TL, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *New England Journal of Medicine* 2009;**361**(8):745-55.

Sun 2013

Sun L, Yu S. Efficacy and safety of denosumab versus zoledronic acid in patients with bone metastases: a systematic review and meta-analysis. *American Journal of Clinical Oncology* 2013;**36**(4):399-403.

Tracz 2006

Tracz MJ, Sideras K, Boloña ER, Haddad RM, Kennedy CC, Uraga MV, et al. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. *The Journal of Clinical Endocrinology & Metabolism* 2006;**91**(6):2011-16.

Trajanoska 2018

Trajanoska K, Schoufour JD, de Jonge EAL, et al. Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: the Rotterdam Study. *Bone* 2018;**114**:116.

Trombetti 2002

Trombetti A, Herrmann F, Hoffmeyer P, et al. Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporosis International* 2002;**13**:731.

Vinogradova 2013

Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. *BMJ* 2013;**346**:f114.

Wells 2008a

Wells G, Cranney A, Peterson J, Boucher M, Shea B, Welch V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal woman. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No: CD004523. [DOI: 10.1002/14651858.CD004523.pub3]

Wells 2008b

Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. [Etidronato para la prevención primaria y secundaria de las fracturas osteoporóticas en mujeres posmenopáusicas]. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No: CD003376. [DOI: 10.1002/14651858.CD003376.pub3] [ISSN:1465-1858]

WHO 2004

World Health Organization. WHO scientific group on the assessment of osteoporosis at the primary health care level. www.who.int.ezproxy.uio.no/chp/topics/Osteoporosis.pdf (accessed 19 November 2007).

Xu 2017

Xu Z. Alendronate for the treatment of osteoporosis in men: a meta-analysis of randomized controlled trials. *American Journal of Therapeutics* 2017;**24**:e130-138.

Yeap 2018

Yeap, BB, Page ST, Grossmann M. Testosterone treatment in older men: clinical implications and unresolved questions from the Testosterone Trials. *The Lancet Diabetes & Endocrinology* 2018;**6**(8):659-72.

Zhou 2016

Zhou J, Wang T, Zhao X, Miller DR, Zhai S. Comparative efficacy of bisphosphonates to prevent fracture in men with osteoporosis: a systematic review with network meta-analyses. *Rheumatology and Therapy* 2016;**3**(1):117-28.

APPENDICES

Appendix 1. Medline search strategy

Ovid MEDLINE(R) ALL <1946 to May 28, 2021>

1 osteoporosis/

2 osteoporo$.tw

3 (osteopenia or osteopaenia).tw

4 (bone adj3 density).tw

5 (bone adj3 mass).tw

6 (bone adj3 loss).tw

7 vertebral deformity.tw1

8 compression.tw

9 crush.tw

10 wedging.tw

11 biconcavity.tw

12 (bone adj1 fragil$).tw

13 (bone adj1 strength).tw

14 bmd.tw

15 (bmc or bone mineral content).tw

16 exp Fractures, Bone/

17 or/1-16

18 Diphosphonates/

19 (bisphosphonate$ or diphosphonate$).tw

20 18 or 19

21 parathyroid hormone/

22 (parathyroid adj2 hormone$).tw

23 "parathyroid hormone[1-34]"/

24 Teriparatide.tw

25 (parathyrin or parathormone).tw

26 (hpth or bpth).tw

27 or/21-26

28 Alendronate/

29 aminohydroxybutane bisphosphonate.tw

30 (Actimax or Adelan or Adronat or Adrovance or Aldren or Aldrion or Aldromax or Aldronac or Aldrox or Alefos or Alehelm or Alenat$ or Alendi$ or Alendo or Alendra$ or Alendris or Alendro$ or Alenic or Alenvir or Alenwin or Aleostito or Alexonal or Aliot or Alovell or Alxis or Ampine or Andante or Arendal or Arthroplus or Aurodren or Berlex or Bestalen or Bifoal Semanal or Bifosa$ or Blindafe or Blocan or Bonacton or Bonal?n or Bonemax or Bonendro$ or Boniran or Brek or Calbion or Calcisedron-D or Caldronate or Caltera or Cleveron or Dargol or Debenal or Defixal or Delfoza or Deparex or Difonate or Discozal or Doryx or Drofaz or Dronadil or Dronal or Dronatex or Dronatifer or Elandur or Eldinir or Endronax or En-Por or Epolar or Filxine or Findeclin or Fixopan or Flamisul or Forosa or Fortimax or Fosal?n or Fosandron or Fosavance or Fosazom or Fosfacid or Fosteo$ or Fostolin or Fosval or Genalen or Gendron or Glamor or Holadren or Jamax-S or Lafedam or Landrolen or Ledronin or Lefosan or Lendral or Lendronal or Leodrin or Lindron or Lozostun or Marvil or Massidron or Maxibone or Maxtral or Minusorb or Moralen or Mosmass or Nafadren or Nichospor or Nofrattil or Nozat or Onclast or Osalen or Osaston or Osdr?n or Oseotenk or Oseum or Ossmax or Osso$ or Ostadil or Ostaham or Ostalert or Ostalon or Ostemax or Ostenan or Ostenil or Osteobon or Osteodur or Osteof$ or Osteomax or Osteomel or Osteonate or Osteonorm or Osteoral or Osteosan or Osteotrat or Ostolek or Ostomax or Pasodron or Phostarac or Porocalm or Porodron or Porosal or Promax or Ralenost or Randronate or Realen or Regenesis or Rekostin or Reyoin or Ridon or Riledron or Romax or Sedron or Semandrol or Silidral or Sinfract or Siranin or Strongos or Synostep or Teiroc or Terost or Tevabone or Tevanate or Tilios or Tivarun or Tonadron or Trabecan or Vegabon or Voroste).tw

31 fosamax.tw

32 or/28-31

33 Risedronate/

34 Risedronic acid/

35 (Acrel or Actokit or Aventis or Alesone or Avestra or Boneact or Ductonar or Juverital or Miosen or Norifaz or Norsed or Nurrid or Optinate or Osteonate or Racidrix or Rentop or Retonel or Ribastamin or Ridron or Risedon or Risedross or Risemyl or Risendros or Riseos or Riseratio or Risofos or Risonate or Rizat or Seralis or Tevanel or Vionate).tw

36 Actonel.tw

37 Atelvia.tw

38 Benet.tw

39 or/33-38

40 Etidronate/

41 Etidronic Acid/

42 (etidronate or Anfozan or Biotredine or Bonemass or Detidron or Didrocal or (didrokit or (didro adj kit)) or Didronat$ or Difosfen or Diphos or Dralen or Dronate-OS or ehdp or ethanehydroxydiphosphonate or Emoform Total or Eopon or Etidrate or Etidrel or Etidron or Etiplus or Feminoflex or Gen-Eti-Cal or Maxibral or Oflocin or Osfo or Ostedron or Osteodidronel or Osteodrug or Osteoto$ or Osteum or Ostogene or Ostopor or Somaflex or Squam or Sterodome or Sviroxit or Tilferan or Tiloetca Combi or Xidifon or xidiphon$.tw

43 didronel.tw

44 or/40-43

45 Ibandronate/

46 ibandron$.tw

47 bm 210955.tw

48 bm210955.tw

49 Bondronat$.tw

50 boniva.tw

51 Bonviva.tw

52 r 484.tw

53 r484.tw

54 or/45-53

55 pamidronic acid/

56 pamidronate$.tw

57 55 or 56

58 zoledronate/

59 (Zoledronic adj2 acid).tw

60 zolendron$.tw

61 zometa.tw

62 reclast.tw

63 zomera.tw

64 aclasta.tw

65 or/58-64

66 Denosumab/

67 prolia.tw

68 xgeva.tw

69 exp RANK Ligand/

70 (rank adj ligand).tw

71 rankligand.tw

72 rankl*.tw

73 or/66-72

74 Romosozumab.tw

75 evenity.tw

76 74 or 75

77 20 or 27 or 32 or 39 or 44 or 54 or 57 or 65 or 73 or 76

78 randomized controlled trial.pt

79 controlled clinical trial.pt

80 (randomized or randomised).ab

81 placebo.ab

82 drug therapy.fs

83 randomly.ab

84 trial.ab

85 groups.ab

86 (double adj blind$).ab

87 or/78-86

88 exp animals/ not humans.sh

89 exp female/ not male.sh

90 87 not 88

91 90 not 89

92 17 and 77 and 91

WHAT'S NEW

Date	Event	Description
8 December 2021	Amended	Minor amendment men with osteoporosis secondary to underlying disease or medication are explicitly excluded from the review

HISTORY

Protocol first published: Issue 8, 2021

CONTRIBUTIONS OF AUTHORS

All authors contributed to the drafting of the protocol.

DECLARATIONS OF INTEREST

Lars Christian Braten: none known

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Teppo Järvinen: none known

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Sami Saku: none known

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