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Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials

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ABSTRACT

OBJECTIVE

To review the comparative effectiveness of osteoporosis treatments, including the bone anabolic agents, abaloparatide and romosozumab, on reducing the risk of fractures in postmenopausal women, and to characterise the effect of antiosteoporosis drug treatments on the risk of fractures according to baseline risk factors.

DESIGN

Systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials.

DATA SOURCES

Medline, Embase, and Cochrane Library to identify randomised controlled trials published between 1 January 1996 and 24 November 2021 that examined the effect of bisphosphonates, denosumab, selective oestrogen receptor modulators, parathyroid hormone receptor agonists, and romosozumab compared with placebo or active comparator.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials that included non-Asian postmenopausal women with no restriction on age, when interventions looked at bone quality in a broad perspective. The primary outcome was clinical fractures. Secondary outcomes were vertebral, non-vertebral, hip, and major osteoporotic fractures, all cause mortality, adverse events, and serious cardiovascular adverse events.

RESULTS

The results were based on 69 trials (>80 000 patients). For clinical fractures, synthesis of the results showed a protective effect of bisphosphonates, parathyroid hormone receptor agonists, and romosozumab compared with placebo. Compared with parathyroid hormone receptor agonists, bisphosphonates were less effective in reducing clinical fractures (odds ratio 1.49, 95% confidence interval 1.12 to 2.00). Compared with parathyroid hormone receptor agonists and romosozumab, denosumab was less effective in reducing clinical fractures (odds ratio 1.85, 1.18 to 2.92 for denosumab *v* parathyroid hormone receptor agonists and 1.56, 1.02 to 2.39 for denosumab *v* romosozumab). An effect of all treatments on vertebral fractures compared with placebo was found. In the active treatment comparisons, denosumab, parathyroid hormone receptor agonists, and romosozumab were more effective than oral bisphosphonates in preventing vertebral fractures. The effect of all treatments was unaffected by baseline risk indicators, except for antiresorptive treatments that showed a greater reduction of clinical fractures compared with placebo with increasing mean age (number of studies=17; β=0.98, 95% confidence interval 0.96 to 0.99). No harm outcomes were seen. The certainty in the effect estimates was moderate to low for all individual outcomes, mainly because of limitations in reporting, nominally indicating a serious risk of bias and imprecision.

CONCLUSIONS

The evidence indicated a benefit of a range of treatments for osteoporosis in postmenopausal women for clinical and vertebral fractures. Bone anabolic treatments were more effective than bisphosphonates in the prevention of clinical and vertebral fractures, irrespective of baseline risk indicators. Hence this analysis provided no clinical evidence for restricting the use of anabolic treatment to patients with a very high risk of fractures.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42019128391.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Treatment options for postmenopausal osteoporosis have increased considerably in the past 20 years

No Cochrane-type reviews or meta-analyses on this topic have been done recently

Treatment of patients at high risk of fractures needs to be looked at and the best interventions identified

WHAT THIS STUDY ADDS

Most approved treatments of postmenopausal osteoporosis for all types of fractures were beneficial, with head-to-head trials favouring bone anabolic treatments over bisphosphonates in the prevention of clinical and vertebral fractures

Overall, the nominal certainty of the evidence was rated down because of the serious risk of bias and risk of imprecision

Results from the meta-regression analysis showed that treatments were beneficial in reducing the risk of fractures in postmenopausal women, and the effect was mostly independent of baseline risk indicators

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Introduction

Advances in research have led to a more accurate assessment of the risk of fractures, and the range of treatment options available to prevent fractures has expanded. Algorithms on the risk of fractures that combine clinical risk factors and bone mineral density are now widely used in clinical practice to target treatment to individuals at high risk of fractures.[1] Although drug treatments targeted at osteoporosis consistently improve bone mineral density, preventing fractures is the most relevant patient outcome.[2] Heterogeneity has been noted for the magnitude of the reduction in the risk of vertebral, non-vertebral, hip, and clinical fractures between treatments. Few active comparator trials have directly compared the effects on fracture endpoints.[3 4] Greater understanding of the differences in the effects of treatments across clinical trials would influence estimates of the benefits of treatment and should therefore be considered among the evidence base that drives guideline recommendations.

Moreover, most randomised controlled trials included patients with an estimated high baseline risk of fractures, but this varied between treatments and over time. Existing post hoc analyses indicate that the antifracture efficacy of some treatments for osteoporosis differ according to estimates of the baseline risk of fractures of individuals in the study, typically, but not exclusively, calculated with the fracture risk assessment tool (FRAX).[5-10] Therefore, factors such as history of fractures, age, bone mineral density, and body mass index, among others, might be potential effect modifiers.

In this analysis, we looked at several baseline risk indicators associated with the efficacy of drug treatments to assess the evidence of the effect and harms of available osteoporosis treatments on primary and secondary reduction of the risk of fractures among postmenopausal women. We also critically appraised the internal validity of the randomised controlled trials.[11] We used meta-regression analyses to explore the evidence of the effect of antiosteoporosis drug treatments on the risk of fracture according to recognised baseline risk factors.

Methods

Our results are reported, and our analyses conducted, in accordance with the guidelines of the Cochrane Collaboration and the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) for Network Meta-Analysis,[12 13] and structured according to the population, intervention, comparison, and outcome framework.[14] The protocol was registered and accepted in March 2019. Minor protocol changes were made: harm outcomes were evaluated post hoc and antiresorptive or bone anabolic drugs were grouped in the meta-regression analyses to increase statistical power.

Eligibility criteria

We considered randomised controlled trials that included postmenopausal women (with no restriction on the definition of sex or gender), with no restriction on age, and where interventions considered bone mineral density or fractures. Because the doses used in randomised controlled trials in Asian settings are different from doses used in the rest of the world, we excluded studies performed exclusively in Asian settings. Trials in mixed populations were included if the data were reported for the populations of interest separately.

The primary outcome was all clinical fractures (excluding fingers and toes), and secondary outcomes were vertebral fractures (clinical, morphometric, or both), non-vertebral fractures, hip fractures, and major osteoporotic fractures, as defined in the randomised controlled trials. Harm outcomes were all cause mortality, number of patients with any adverse events, and number of patients with serious cardiovascular adverse events. The time frame was the longest follow-up after the start of the preplanned intervention. Interventions considered for inclusion were bisphosphonates (alendronate, risedronate, ibandronate, and zoledronate), denosumab, selective oestrogen receptor modulators (raloxifene hydrochloride, bazedoxifene, and bazedoxifene with conjugated oestrogen), parathyroid hormone receptor agonists (teriparatide and abaloparatide), and sclerostin inhibitor (romosozumab). Studies were included if they examined the effects compared with placebo or with an active comparator. Calcium and vitamin D supplementation were allowed as co-interventions. Studies examining sequential treatment or combination treatment were also considered for inclusion. No restrictions were set on dose or length of treatment. The baseline risk indicators considered were previous history of fractures, mean age, mean spine T score, mean body mass index, and mean FRAX score for major osteoporotic fractures.

Information sources and search strategy

One of the authors (MNH) performed the literature search on 24 November 2021. Databases searched were Medline and Embase via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL)[15] (acceptable coverage for musculoskeletal disorders has been shown[16]). The search strategy (table S1) included medical subject headings and text words related to the population, intervention, comparison, and outcome framework, and was restricted to human and published studies written in English from 1 January 1996 onwards. Reference lists of previous published systematic reviews and meta-analysis, and of the included studies were screened. Content experts ensured that any relevant studies were not missed by the search.

Selection of studies

Duplicates were identified and excluded in EndNote. The remaining references were imported to Covidence (www.covidence.org/home); two reviewers independently screened titles and abstracts, followed

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by screening of the full text. Disagreements were resolved by discussion. Conference abstracts were considered if data were not published elsewhere.

Data extraction

Study data were extracted with a predefined extraction template in Covidence. Extraction of background data was performed by one reviewer and extraction of quantitative data was independently performed by two reviewers. Disagreements were resolved by discussion. Information from journal article(s), conference abstract(s), trial protocol, or trial registry record was used as sources in the data extraction and the risk of bias assessment. Authors were contacted by email to provide more information to resolve uncertainties or obtain missing data (table S2). No deadlines were given. One author provided data on hip fractures among postmenopausal women.[17] When multiple reports of one study were identified, the publication with the longest follow-up and the most complete data was included, and if all studies had complete information, these studies were treated as one study with reference made to all of the publications. Intention-to-treat analyses were prioritised in the data extraction. In multi-arm trials, results from treatments that were the same but at various doses were combined into one group. In four studies,[18-21] missing data on lumbar spine bone mineral density T score were replaced with estimates calculated by Bouxsein et al.[22]

Critical appraisal of reporting in individual studies

The Cochrane risk of bias tool 2[23] (parallel trials) was used for critical appraisal of the reporting of the included studies. Two reviewers independently conducted a risk of bias appraisal. Discrepancies were resolved by discussion.

Statistical analysis

For the meta-analysis, dichotomous outcomes were analysed by calculating the relative risk for the direct comparisons (with 95% confidence intervals). Relative risk was also converted into the corresponding anticipated absolute risk in the study population, for each 1000 individuals,[24] calculated as the difference between the baseline risk of the outcome (median in the control group) and the risk of outcome after the intervention was applied. The I^2 statistic was used to measure the proportion of total variability caused by heterogeneity between the trials.[25] Heterogeneity between studies was quantified by the estimate τ^2. An inverse variance random effects model was applied as the default to allow for heterogeneity in treatment effects across trials.

Subgroup analysis by risk of bias was planned but was not considered feasible because most of the included studies were rated as having some concerns or had a high risk of bias. The meta-analyses, funnel plots, and forest plots were produced in Review Manager Software (version 5.2, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Statistical power is usually too low to distinguish chance from real asymmetry, so we did not perform any tests for funnel plot asymmetry because most of the meta-analysis subgroups were based on <10 trials (data points).

In a network meta-analysis, when two or more drugs are compared with a common standard, the difference in effect between these drugs with respect to the common standard forms the basis of indirect comparisons (ie, formation of a star network). In our analysis, most drug treatments were compared with placebo and the same baseline treatment. We used the star design[26] for indirect treatment comparisons and included one active and one placebo group from each available trial, independent of concomitant drug treatment use.[27] To analyse fracture outcomes, we calculated odds ratios by default after use of a random effects network meta-analysis model with binomial likelihood and logit link. For the primary (arm based) network meta-analyses, we used generalised linear mixed models combining a series of 2×2 tables, with the odds ratio modelled as a linear combination of study level covariates and random effects, representing variation between studies.[28] Although the prior choice for heterogeneity between studies is critical in bayesian network meta-analysis with empirical Bayes methods,[29] the prior probability distribution for heterogeneity between studies is estimated from the data.[30] Fitting the network meta-analysis model estimates the summary treatment effects for each drug relative to others, allowing for clustering of patients and drugs within trials, and for heterogeneity between trials in treatment effects (as measured by τ^2, assuming the same for every treatment effect). Furthermore, to assess the robustness of these results, we performed sensitivity analyses adjusting each group for the length of the study multiplied by the specific number of participants randomly allocated (ie, a proxy for patient years).

We ranked clinical efficacy with rankograms, surface under the cumulative ranking, and average ranks. The transitivity assumption was evaluated by comparing the distribution of clinical and methodological variables that could act as effect modifiers, whereas statistical consistency (ie, agreement between direct and indirect evidence) was evaluated with node splitting.

In the meta-regression analysis, for each combination of outcome and baseline risk indicator, we performed a meta-regression with restricted maximum likelihood estimation as part of mixed linear models. The resulting slope β indicates the increase (or decrease) in treatment effect in terms of log risk ratio. For ease of interpretation, we used back transformation, so the slope is interpreted as the proportional increase (or decrease) in the treatment effect (ie, risk ratio) per unit increase in the baseline risk indicator. A slope of $\exp(\beta)=1$ indicates no association with the treatment effect. For brevity, $\exp(\beta)$ is β.

We performed separate analyses by type of treatment and comparator group in the following groups to increase statistical power: antiresorptive

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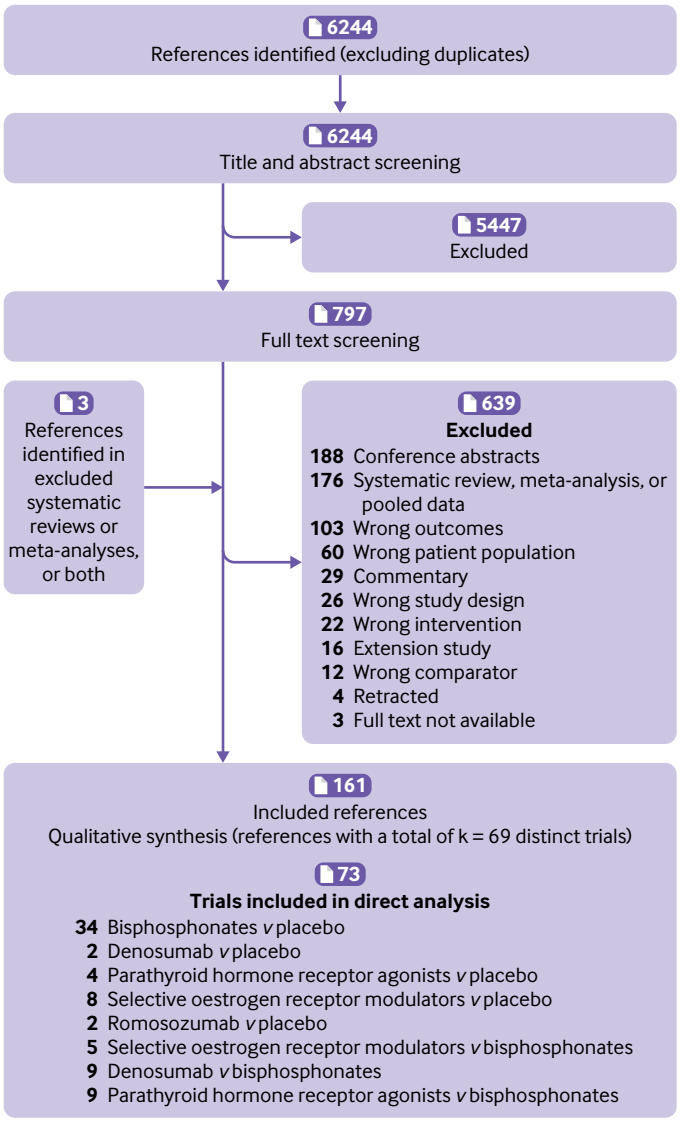

Fig 1 | Flowchart of included studies. Numbers=number of records; k=number of distinct trials

drugs (selective oestrogen receptor modulators, bisphosphonates, and denosumab) versus placebo; bisphosphonates versus placebo; anabolic treatments (romosozumab and parathyroid hormone receptor agonists) versus placebo; and anabolic treatments (romosozumab and parathyroid hormone receptor agonists) versus bisphosphonates. We quantified inconsistency across trials with the standard I^2 statistic, describing the percentage of total variation caused by heterogeneity rather than chance.[31] We estimated the variation explained by each baseline risk indicator by $\%\tau^2_{explained}=(\tau^2_0-\tau^2)/\tau^2_0\times100\%$, where τ^2_0 is the variation between trials for the meta-regression without the baseline risk indicator in the model. Statistical analyses were performed in R (version 3.6.1)[32 33] and SAS (version 9.4). Grading of recommendations, assessment, development, and evaluations (GRADE) fitted to the network meta-analysis was used to rate the overall certainty of evidence for each outcome.[34]

Patient and public involvement

Owing to lack of funding, patients and members of the public were not involved in the design, conduct, or reporting of this study.

Results

Technical assessment

Literature search and study selection

We identified 6244 records after removing duplicates. Screening of titles and abstracts excluded 5447 records, and in the remaining 797, the full text was screened, resulting in exclusion of 639 references. When references were screened, we identified three more records eligible for inclusion. Table S3 lists the reasons for exclusion. In total, we identified 161 references[3 4 5 7-10 17-21 35-183] providing information about 69 distinct trials. Figure 1 is a flowchart of the included studies.

Study characteristics

The included studies were published between 1 January 1996 and 24 November 2021. Table S4 provides a further description of the included studies. Table S5 details the role of funding sources and potential conflicts of interest.

Data completeness

Thirty four studies reported on clinical fractures, 40 reported on vertebral fractures, 52 on non-vertebral fractures, 30 on hip fractures, and nine studies reported on major osteoporotic fractures. For data completeness for the baseline risk indicators, 52 studies reported on a history of fractures (75%), all studies reported mean age (100%), 49 studies reported spine T scores (71%), 51 studies reported body mass index (74%), and six studies reported FRAX scores (9%). The prevalence of a history of fractures ranged from 0 to 100% in the study populations, mean age from 51.5 to 85.5 years, mean spine T score from −0.4 to −3.9, mean body mass index from 23.7 to 29.1, and mean FRAX score for the probability of a major osteoporotic fracture within the next 10 years from 13.2% to 30%.

Certainty of evidence

The overall GRADE evaluation of the certainty in the effect estimates was moderate to low for all individual outcomes because of the serious risk of bias and imprecision (table 1 and secondary outcomes in table S6).

The serious risk of bias was mainly because of unclear reporting of how random sequence and allocation concealment were performed (table S7). Some studies also had incomplete outcome data[74 83 105 129 145 151] and selective outcome reporting[74 83 105 129 145 151] (table S7). Potential involvement of the funding parties was judged to increase the risk of bias related to conflict of interest. A serious risk of imprecision was assigned for outcomes where data were available from one study only. From visual inspection of the funnel plots, we did not detect evidence of small study effects (fig S1).

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Table 1 | Estimates of effects and quality ratings for comparison of drug treatments for osteoporosis to prevent clinical fractures

	Direct evidence		Network meta-analysis	
Comparison	Relative risk (95% CI)	Absolute risk difference* (95% CI)	Odds ratio (95% CI)	Certainty of evidence
Parathyroid hormone receptor agonists *v* placebo	0.58 (0.35 to 0.95)	35 fewer per 1000 (39 fewer to 3 fewer)†	—	Moderate¶
Selective oestrogen receptor modulators *v* placebo	0.41 (0.10 to 1.69)	—	—	Low¶ **
Romosozumab *v* placebo	0.64 (0.47 to 0.89)	9 fewer per 1000 (13 fewer to 3 fewer)‡	—	Low¶ **
Parathyroid hormone receptor agonists *v* bisphosphonates	0.61 (0.39 to 0.94)	—	—	Moderate¶
Denosumab *v* bisphosphonates	1.28 (0.91 to 1.81)	—	—	Low¶ **
Romosozumab *v* bisphosphonates	0.82 (0.68 to 0.99)	—	—	Low¶ **
Romosozumab *v* parathyroid hormone receptor agonists	0.88 (0.32 to 2.37)	—	—	Low¶ **
Bisphosphonates *v* denosumab	—	—	0.81 (0.57 to 1.15)	Low¶ **
Bisphosphonates *v* placebo	0.81 (0.72 to 0.91)	14 fewer per 1000 (21 fewer to 7 fewer)§	0.79 (0.70 to 0.89)	Moderate¶
Bisphosphonates *v* parathyroid hormone receptor agonists	—	—	1.49 (1.12 to 2.00)	Moderate¶
Bisphosphonates *v* romosozumab	—	—	1.26 (0.99 to 1.60)	Low¶ **
Bisphosphonates *v* selective oestrogen receptor modulators	0.96 (0.48 to 1.94)	—	1.40 (0.72 to 2.71)	Low¶ **
Denosumab *v* placebo	3.08 (0.42 to 22.33)	—	0.98 (0.68 to 1.41)	Low¶ **
Denosumab *v* parathyroid hormone receptor agonists	—	—	1.85 (1.18 to 2.92)	Moderate¶
Denosumab *v* romosozumab	—	—	1.56 (1.02 to 2.39)	Moderate¶
Denosumab *v* selective oestrogen receptor modulators	—	—	1.74 (0.82 to 3.66)	Low¶ **
Placebo *v* parathyroid hormone receptor agonists	—	—	1.90 (1.41 to 2.55)	Moderate¶
Placebo *v* romosozumab	—	—	1.60 (1.24 to 2.05)	Low¶ **
Placebo *v* selective oestrogen receptor modulators	—	—	1.78 (0.91 to 3.47)	Low¶ **
Parathyroid hormone receptor agonists *v* romosozumab	—	—	0.84 (0.59 to 1.21)	Low¶ **
Parathyroid hormone receptor agonists *v* selective oestrogen receptor modulators	—	—	0.94 (0.46 to 1.93)	Low¶ **
Romosozumab *v* selective oestrogen receptor modulators	—	—	1.11 (0.55 to 2.25)	Low¶ **

CI=confidence interval.
*Absolute measure of intervention effects is difference between baseline risk of outcome (median in control group) and risk of outcome after intervention is applied.
Baseline risk calculated from: †Miller 2016,[120] ‡Cosman 2016,[61] §Greenspan 2003.[86]
Downgraded because of ¶serious risk of bias or **imprecision.[34]

Clinical efficacy

Synthesis of results

All osteoporosis treatments had at least one placebo controlled trial, and all treatments were directly compared with at least one active drug in any of the networks (fig 2), except in the analyses of major osteoporotic fractures. Figure 3 and figure 4 show the results from the network meta-analysis for all outcomes. Table S8 shows the sensitivity analyses. Figure S4, table S9, and table S10 present the rankogram, mean ranks, and surface under the cumulative ranking values that summarise the evidence and comparisons. Parathyroid hormone receptor agonists had the highest rankogram and surface under the cumulative ranking value, and the lowest mean rank, indicating better ranking of the treatment (fig S4).

Figure 5 is a forest plot illustrating the results of node splitting, comparing the direct, indirect, and network estimates. For our network meta-analysis, we found no indication of inconsistency between direct and indirect evidence (fig 5), and we considered that the relevant effect modifiers were balanced across the different comparisons. Figure S3 reports the potential baseline risk indicators facilitating the judgments about the assumption of transitivity.

Clinical fractures (prespecified primary outcome)

For clinical fractures, the network meta-analysis showed a protective effect of bisphosphonates, parathyroid hormone receptor agonists, and romosozumab compared with placebo, but not of denosumab and selective oestrogen receptor modulators (fig 3). Analysis of the data for denosumab did not include the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) pivotal trial, however, because of lack of aggregated data for clinical fractures in the publication. Compared with parathyroid hormone receptor agonists, bisphosphonates were less effective in reducing clinical fractures (odds ratio for

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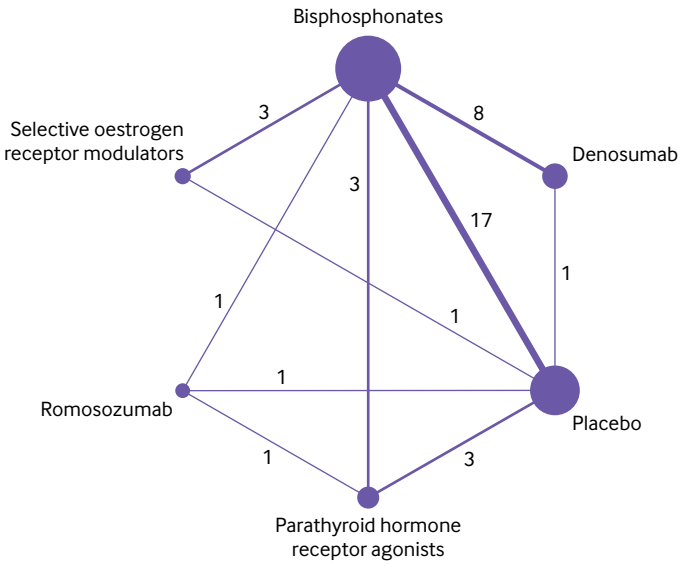

Fig 2 | Network plot of studies included in network meta-analysis on clinical fractures. Each circle represents an intervention and is referred to as a node. Nodes are sized proportionally to the number of trials that included each intervention. Lines between nodes represent direct comparisons, and their thickness is proportional to the number of trials contributing to each comparison. Number of trials for each direct comparison is shown. No connecting line between two treatments indicates no direct comparison

bisphosphonates *v* parathyroid hormone receptor agonist 1.49, 95% confidence interval 1.12 to 2.00). Compared with parathyroid hormone receptor agonists and romosozumab, denosumab was less effective in reducing clinical fractures (odds ratios for denosumab *v* parathyroid hormone receptor agonist1.85, 95% confidence interval 1.18 to 2.92 and *v* romosozumab 1.56, 1.02 to 2.39). The results were robust after adjustment for patient years (table S8).

Vertebral fractures (secondary outcome)

We found an effect of all treatments on vertebral fractures compared with placebo. In the active treatment comparisons, denosumab, parathyroid hormone receptor agonists, and romosozumab were more effective in preventing vertebral fractures than bisphosphonates (fig 3). The results were robust to adjustment for patient years (table S8).

Non-vertebral fractures (secondary meta-analysis outcome)

Network meta-analyses could not be performed for non-vertebral fractures.

Hip fractures (secondary outcome)

The network meta-analysis showed a protective effect of bisphosphonates, denosumab, parathyroid hormone receptor agonists, and romosozumab for hip fractures compared with placebo, but not of selective oestrogen receptor modulators (fig 3). In the active treatment comparisons, romosozumab was more effective in preventing hip fractures than oral bisphosphonates or selective oestrogen receptor modulators (fig 3). The results were robust to adjustment for patient years (table S8).

Major osteoporotic fractures (secondary outcome)

This outcome was reported in only a small number of trials, which limited the power of the analysis. For major osteoporotic fractures, the network meta-analysis showed a protective effect of bisphosphonates, parathyroid hormone receptor agonists, and romosozumab compared with placebo, but not of denosumab or selective oestrogen receptor modulators (fig 3). We found no differences in the active treatment comparisons.

Safety outcomes

Compared with placebo or other comparators, the active treatments did not increase the risk of all cause mortality, number of patients with any adverse events, or number of patients with serious cardiovascular adverse events (fig 4 and table S8).

Meta-regression analyses

The effect of all treatments was unaffected by the baseline risk indicators (table S11), except for antiresorptive treatments that showed a greater reduction of clinical fractures compared with placebo with increasing mean age (β=0.98, 95% confidence interval 0.96 to 0.99, $\tau^2_{explained}$=97%, P=0.031, based on 17 studies) (fig 6 and table S11).

Discussion

Treatment options for postmenopausal osteoporosis have increased considerably in the past 20 years. No Cochrane-type reviews or meta-analyses on this topic, however, have been done recently.[184 185] Although effective, relatively safe, and affordable treatments are available,[186-199] the treatment of patients at high risk of fractures needs to be looked at and the best interventions identified. Our network meta-analyses support a beneficial effect of most, but not all, treatments on all fracture outcomes compared with placebo. These treatments have already been approved by the appropriate authorities in Europe, the US, and elsewhere for the treatment of postmenopausal osteoporosis.

Although most randomised controlled trials have preferentially included patients with a high baseline risk of fractures, the prevalence of these patients has varied between different treatments and studies. Higher baseline risk is a major factor for the absolute risk of fractures, but in most studies the relative reduction in the risk of fractures was found to be mostly independent of baseline risk factors. Confirmation that the approved treatments reduce the risk of fractures compared with placebo is not surprising, but whether all treatments are equally effective is an interesting question. The network meta-analyses showed that bone anabolic treatments (teriparatide[62 63 83 89 129 200] and romosozumab[4 113]) reduced the risk of clinical and vertebral fractures compared with bisphosphonates. The certainty of the pooled results on bone anabolic treatments, especially romosozumab, however, was found to be low because of the small number of studies identified.

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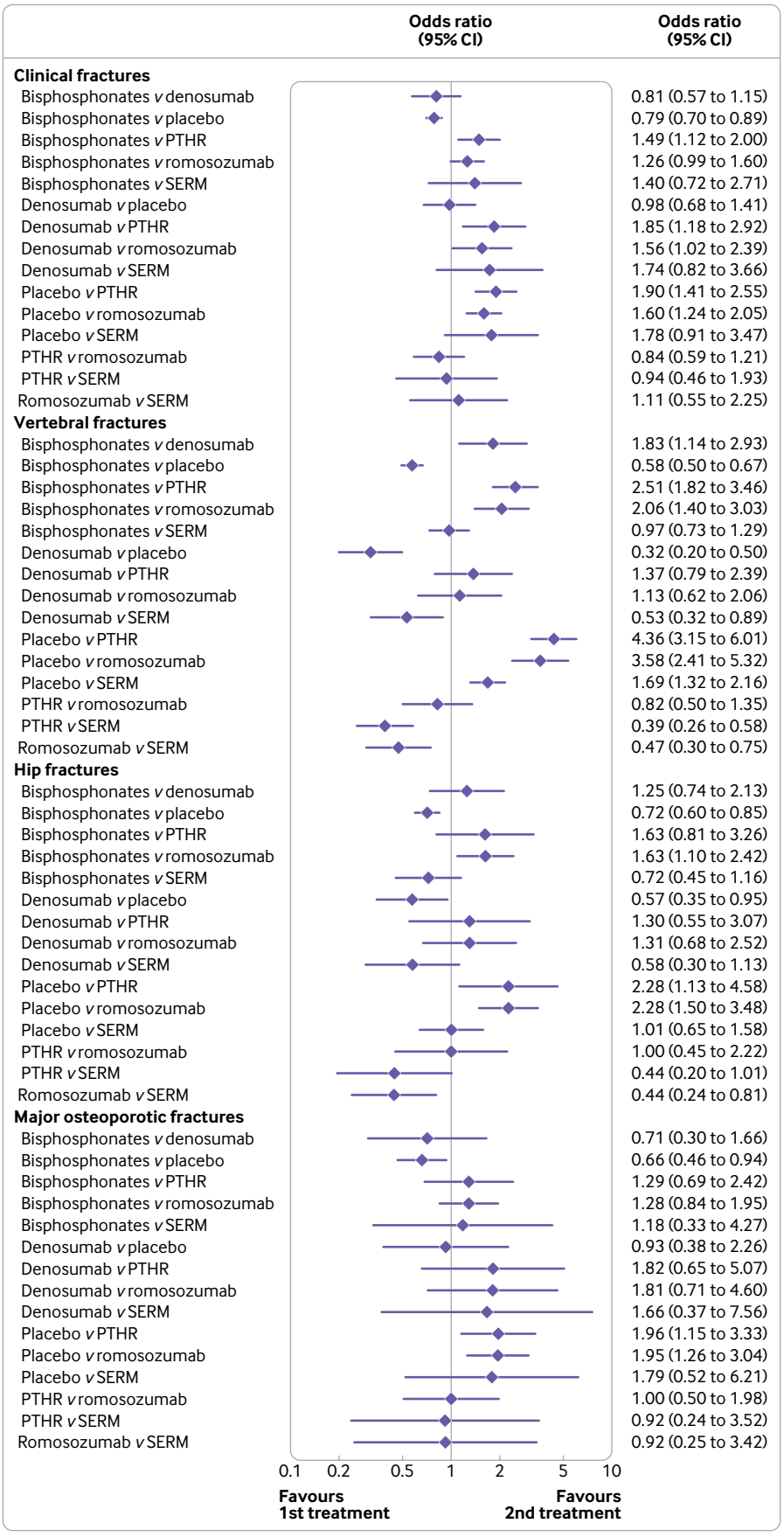

Fig 3 | Network meta-analysis for clinical, vertebral, hip, and major osteoporotic fractures. PTHR=parathyroid hormone receptor agonists; SERM=selective oestrogen receptor modulators; CI=confidence interval

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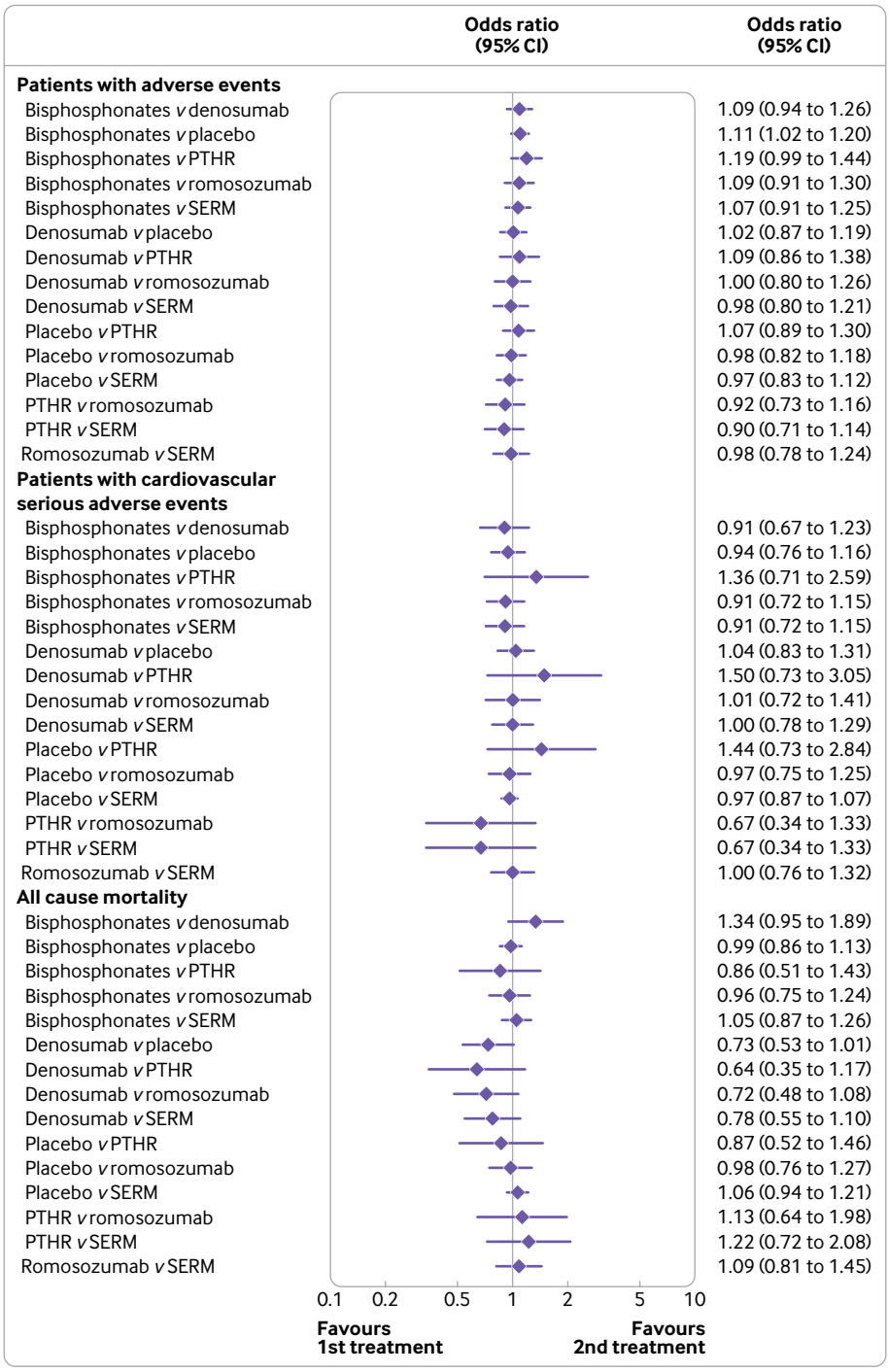

Fig 4 | Network meta-analysis for safety outcomes. PTHR=parathyroid hormone receptor agonists; SERM=selective oestrogen receptor modulators; CI=confidence interval

Head-to-head randomised controlled trials are more challenging than studies comparing active treatment with placebo. In head-to-head trials, the number of individuals with fractures is much lower, and therefore these studies might have low statistical power and are also unlikely to be replicated because of the financial and operational challenges. Hence most head-to-head randomised controlled trials were done comparing anabolic and antiresorptive treatments, where a clinically relevant difference in antifracture efficacy was anticipated.

Because of the lack of consistent reporting on non-vertebral fractures, hip fractures, and major osteoporotic fractures across studies, we could not draw more definite conclusions. The VERO (VERtebral fracture treatment comparisons in Osteoporotic women) trial is an illustrative example of the effect of different definitions of groups of fractures. When non-vertebral major osteoporotic fractures were defined according to the European Medicine Agency (hip, radius, humerus, ribs, pelvis, femur, and tibia), the reduction seen with teriparatide compared with

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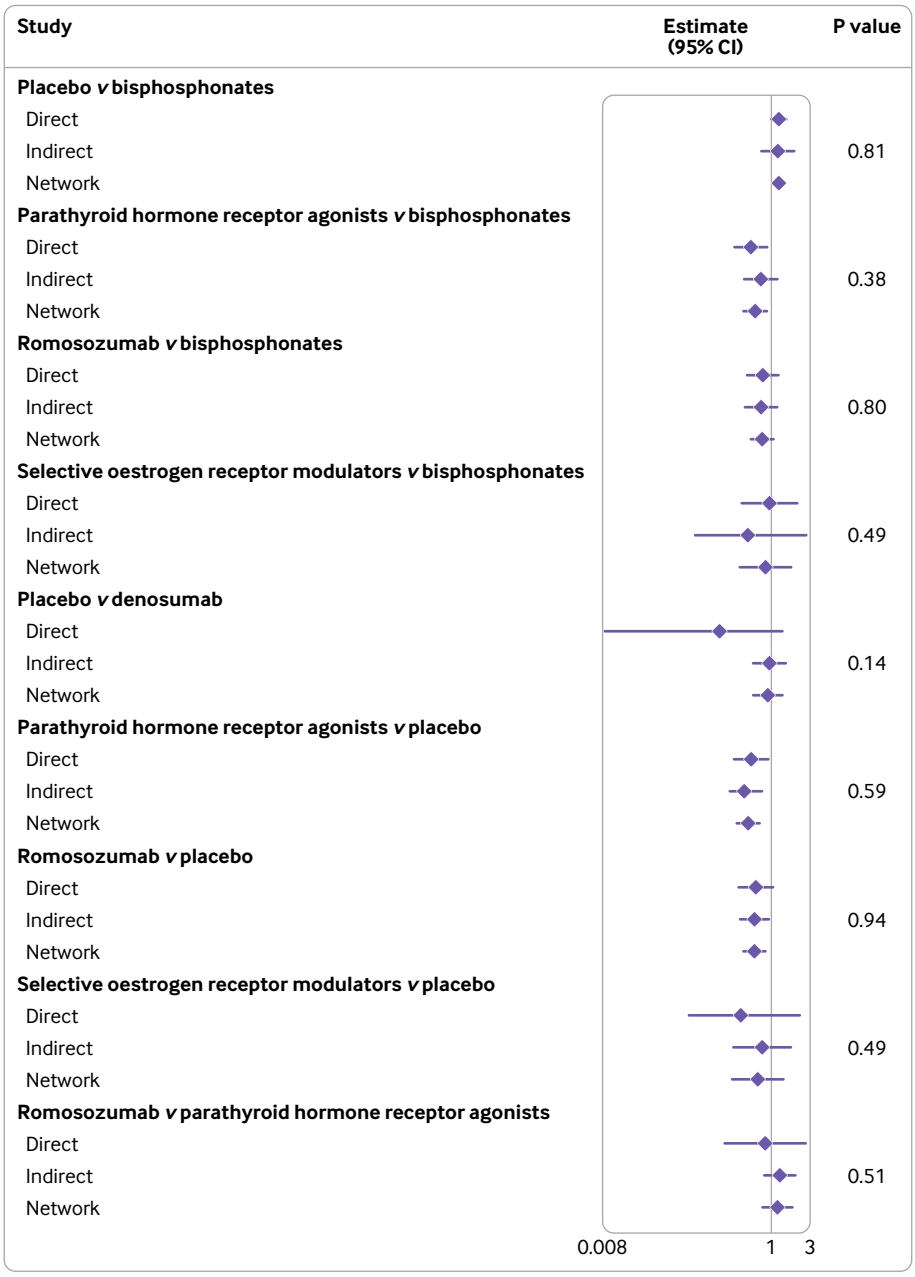

Fig 5 | Forest plot illustrating the result of node splitting, comparing direct, indirect, and network estimates. CI=confidence interval

risedronate was not significant, but when major osteoporotic fractures were defined according to FRAX (clinical, vertebral, hip, humerus, and forearm fractures), the reduction was significant (hazard ratio 0.40, P<0.001).[168] Estimates for non-vertebral, hip, and major osteoporotic fractures were somewhat uncertain because of low statistical power and varying definitions, but the results were largely in agreement with estimates for clinical and vertebral fractures.

Meta-regression analysis

The benefits of antiresorptive agents in general, and bisphosphonates in particular, as well as bone anabolic treatments, seemed to be independent of baseline risk indicators at the study level. Nevertheless, the meta-regression analyses showed that antiresorptive treatments (bisphosphonates, selective oestrogen receptor modulators, and denosumab) seemed more effective in reducing the risk of clinical fractures with increasing mean age (mean age reported in studies ranged from 50 to 85 years), indicated by the estimated slope <1 and that including mean age in the model reduced the variance between studies. This observation is important because a common belief is that the oldest patients might not benefit from osteoporosis treatment, whereas the evidence provided here suggests that antiresorptive treatments might be even more effective in reducing clinical fractures in this high risk population. The results of the meta-regression are vulnerable to aggregation bias and study level confounding, however, and need to be confirmed in studies of individual patient data.

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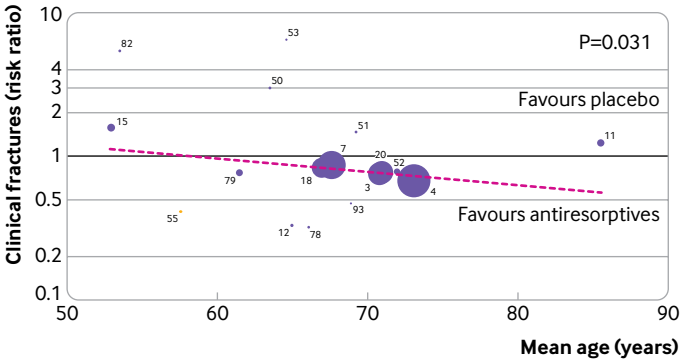

Fig 6 | Meta-regression on risk of clinical fractures with baseline mean age as risk indicator, for antiresorptive agents (selective oestrogen receptor modulators, bisphosphonates, and denosumab) versus placebo. Based on restricted maximum likelihood based meta-regression for association between (log risk ratio) clinical fractures and mean age. Bisphosphonates versus placebo are indicated by purple dots and selective oestrogen receptor modulators versus placebo by yellow dot; colours do not reflect the applied model and are only for illustrative purposes. Meta-regression was done on log risk ratio scale, but for ease of interpretation, the back transformed risk ratio is shown. Identification number in figure, trial name, and reference: 3=FIT1 (Fracture Intervention Trial 1)[18]; 4=HORIZON-PFT (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial)[19]; 7=FIT2 (Fracture Intervention Trial 2)[20]; 11=ZEST (Zoledronic acid in frail Elders to STrengthen bone)[85]; 12=ACTRN12607000576426[87]; 15=Hosking 1998[21]; 18=IBAN IV[183]; 20=ACTRN1260900593235[139]; 50=ACTRN12605000278639[88]; 51=Hosking 2003[93]; 52=Greenspan 2003[86]; 53=Downs 2000[73]; 55=Miller 2008[121]; 78=Bell 2002[44]; 79=Bone 2000[49]; 82=McClung 2009[182]; 93=NCT00271713[165]

Bone anabolic treatments reduced the risk of fractures more than antiresorptive agents in postmenopausal women, and their comparative efficacy was largely independent of baseline risk indicators. The results for bone anabolic treatments were based on seven included studies, however, and only a modest spread of risk factors between studies was found, making it more difficult to detect these associations. Individual comparison trials have shown the greater benefits of teriparatide or romosozumab compared with oral bisphosphonates alone in high risk groups, characterised by 100% presence of vertebral fractures at baseline.[34 83] Our data suggest that the advantage of bone anabolic treatment versus antiresorptive treatment might not be restricted to the highest risk groups. The reason for recommending bone anabolic treatments specifically in patients at high risk of fractures is therefore based more on cost considerations (ie, lower cost per fracture avoided if the fracture rate is high) than on robust evidence favouring its use in this group over others. With the introduction of biosimilars and generics of teriparatide at a lower cost, our results could prompt a review of current guidelines for an earlier use of these agents in the treatment of osteoporosis.

Strengths and limitations of included studies

We used standardised methods allowing us to evaluate the certainty of the results. The potential risks of bias identified across several of the included studies, predominantly in the form of selective reporting, lowered the rate of certainty in the effect estimates of the outcomes. Other reporting items might have favoured newer studies because older studies would not always have anticipated a future standard. Reporting items that might have favoured newer studies were domains related to the description of randomisation sequence generation and allocation concealment (selection bias), but not the domains related to incomplete outcome data, selective outcome reporting (post hoc analyses), and potential active involvement of funding parties. We adhered to best practice and reviewed only the quality of published scientific papers. The supposedly poor quality of reporting in randomised controlled trials is not unique to drug trials of osteoporosis and is a common problem across medical disciplines.[201 202] Efforts towards more transparent and stringent reporting are urgently needed.

Strengths and limitations of systematic review

Along with the 2020 update to the Endocrine Society's guidelines for the treatment of postmenopausal osteoporosis,[203 204] our analysis included the recently launched drugs, abaloparatide and romosozumab, and presented an up-to-date and comprehensive systematic review of all available head-to-head trials in this field. A major strength of our systematic review was that the methods were rigorous and transparent, with a priori defined criteria in accordance with standardised guidelines. Other strengths were the large number of randomised controlled trials included and restriction of our patient population to postmenopausal women, which ensured robust results and reduced the heterogeneity caused by sex and comorbidity.

The network meta-analysis and meta-regression analysis were limited by a substantial amount of missing data on outcomes and baseline risk indicators of interest, which required combining treatment groups on an ad hoc basis to make the best use of the number of data points. Also, we did not differentiate between outcomes reported as adverse events, or primary or secondary outcomes, resulting in various and non-standardised definitions of fractures across studies. In our network meta-analysis, denosumab did not significantly reduce the risk of clinical fractures compared with placebo. Critically, the FREEDOM study from 2009, which was pivotal for almost all approvals made for denosumab, did not provide the outcomes included in the analysis. We cannot exclude the possibility that data on adverse events could have been inadequately monitored and infrequently reported, further introducing bias. Because we relied on published mean baseline characteristics, instead of individual patient data, a risk of aggregation bias exists that could increase or decrease the associations found. Furthermore, meta-regression analyses, despite including only randomised controlled trials, are observational and the results might be confounded by other characteristics.[205] Interpretation might also be complicated by overlapping outcomes (eg, in some studies non-vertebral fractures would also count as clinical fractures[80 87 104]) and overlapping treatment groups.

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Directions for future research

Future research could include individual patient data from the trials to advance our understanding of the influence of baseline risk indicators on the efficacy of treatments. Progress has been made for antiresorptive treatments by the Foundation for the National Institutes of Health Bone Quality project, where individual patient data were collected for 28 000 participants in 11 trials of bisphosphonates and selective oestrogen receptor modulators.[206] We encourage randomised controlled trial data to be made available to provide the evidence needed for a personalised approach to the management of osteoporosis.

Conclusion

The current available evidence indicates that, despite the varying quality of the reported studies, most approved treatments for postmenopausal osteoporosis are beneficial for all types of fractures, with head-to-head trials favouring bone anabolic treatments over bisphosphonates in the prevention of clinical and vertebral fractures, and romosozumab followed by alendronate over alendronate in the prevention of hip fractures in patients at high risk of fractures. Overall, the nominal certainty in the evidence was rated down based on the GRADE criteria because of the serious risk of bias across all treatment combinations and outcomes. For the bone anabolic treatments, a risk of imprecision also existed because only a few studies were available.

The results of the meta-regression analysis showed that treatments were beneficial in reducing the risk of fractures in postmenopausal women, and the effect was mostly independent of baseline risk indicators. Treatment with bone anabolic agents effectively reduced clinical and vertebral fractures, irrespective of mean age and baseline risk, whereas antiresorptive treatments seemed more effective in older patients. Because bone anabolic treatments were more effective than bisphosphonates, irrespective of the baseline risk, no evidence from clinical trials exists supporting the view that bone anabolic treatment should be limited to patients at very high risk of fractures because of efficacy.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: This research will be reported in press releases and presented at scientific meetings, including the Cochrane Colloquium. The research will be shared with the Committee of National Societies of the International Osteoporosis Foundation (IOF) for communication to patient societies.

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Web appendix: Supplementary material

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