
Article:
Simpson, E. orcid.org/0000-0001-7353-5979, Martyn-St James, M., Hamilton, J. et al. (4 more authors) (2020) Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures : a systematic review and network meta-analysis. Bone, 130. ISSN 8756-3282

https://doi.org/10.1016/j.bone.2019.115081

Clinical effectiveness of denosumab, raloxifene, romosozumab, and teriparatide for the prevention of osteoporotic fragility fractures: a systematic review and network meta-analysis

Keywords: Osteoporosis; Systematic review; Network meta-analysis; Fragility fracture; anti-resorptive agents; bone-forming agents.

Abstract

Objectives: To determine the clinical effectiveness of denosumab (DEN), raloxifene (RLX), romosozumab (ROMO) and teriparatide (TPTD), within their licensed (or anticipated licensed) indications, for the treatment of osteoporosis.

Methods: A systematic review was conducted. Nine electronic databases and trial registries were searched up to the end of July 2018. Studies were eligible for inclusion if they were randomised controlled trials (RCT) in a population at risk of osteoporotic fracture, comparing these four non-bisphosphonates DEN, RLX, ROMO, or TPTD with each other, a non-active treatment, or the bisphosphonates alendronate (ALN), risedronate (RIS), ibandronate (IBN) and zoledronic acid (ZOL). Quality of included studies was assessed using the Cochrane Risk of Bias tool. Network meta-analyses (NMA) were used to determine the relative effectiveness of treatments.

Results: The systematic review identified 7,898 citations. Forty-six RCTs of non-bisphosphonates met the inclusion criteria for the review and provided data for analyses. Additionally 49 RCTs of bisphosphonates were used in the NMAs. Forty-six RCTs were included in the NMA of vertebral fracture data, 23 RCTs for hip fractures and 73 RCTs in the NMA of femoral neck bone mineral density (FN BMD). For vertebral fractures, all four non-bisphosphonates showed statistically significant benefit relative to placebo: TPTD HR 0.23 (95% credible internal (CrI) 0.16, 0.32); ROMO followed by ALN 0.25 (95% CrI 0.15, 0.43); DEN HR 0.30 (95% CrI 0.21, 0.43); RLX HR 0.61 (95% CrI 0.44, 0.80). The four non-bisphosphonates interventions studied also showed statistically significant benefit relative to placebo for FN BMD, and for hip fractures TPTD, ROMO followed by ALN, and DEN showed statistically significant benefit relative to placebo.

Conclusions: The four non-bisphosphonate interventions studied were all clinically effective for reducing vertebral fractures when compared to placebo, and were beneficial for change in FN BMD compared to placebo. TPTD, ROMO followed by ALN, and DEN reduced hip fractures.

1. Introduction

The World Health Organization defines osteoporosis as low bone mass and microarchitectural deterioration of bone tissue, with consequent bone fragility and increased susceptibility to fracture. (1) Osteoporotic, or fragility, fractures can be considered those that result from low energy trauma that would not ordinarily result in fracture, or alternatively the type of fracture that increases with frequency the lower the bone mineral density.(2) Low energy trauma may be quantified as forces equivalent to a fall from standing height or less.(1, 3)

Hip fractures are a major concern as they are associated with high rates of disability (50%) and mortality (20%), however these are rarely the primary endpoints of trials, with the more commonly occurring vertebral fracture more readily allowing statistically significant differences between groups to be shown. (3) (4) There is an established association between vertebral fractures and both bone mineral density (BMD) and other osteoporotic fractures.(2, 3) Fragility fractures can cause pain and disability, impacting health-related quality of life, and vertebral fractures are associated with curvature of the spine and height loss, and decreased life expectancy. (1, 3)

Treatments for osteoporosis include the anti-resorptive agents bisphosphonates, denosumab (DEN), raloxifene (RLX); and bone-forming agents teriparatide (TPTD) and romosozumab (ROMO). This review formed part of a wider project looking at non-bisphosphonates for the prevention of osteoporotic fragility fractures, that included non-vertebral fracture and adverse event data as well as an evaluation of cost-effectiveness.(5) The objective of the present study was to assess the clinical effectiveness of the non-bisphosphonates DEN, RLX, ROMO, and TPTD. This was addressed by systematic review of the evidence, and conducting a network meta-analysis (NMA) of these non-bisphosphonates, non-active treatment, and the bisphosphonates alendronate (ALN), risedronate (RIS), ibandronate (IBN) and zoledronic acid (ZOL).

2. Materials and methods

2.1 Review methods

A systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(6) (7) A comprehensive search was undertaken to systematically identify clinical effectiveness literature relating to the non-bisphosphonates DEN, RLX, ROMO, and TPTD, and the comparator bisphosphonates ALN, IBN, RIS and ZOL, within their European Medicines Agency (EMA) licensed indications for the prevention of osteoporotic fragility fractures. At the time of searches, ROMO was under application to the EMA. The decision was taken to include ROMO for one year, or the sequence of therapy ROMO for one year followed by anti-resorptive (its anticipated licensed indication (and, following searches, in line with the Food and Drug Administration licence 2019) (8)). Searches were undertaken in the following databases up to the end of July 2018: MEDLINE (via Ovid); Embase (via Ovid); Cochrane Database of Systematic Reviews; Database of Abstract of Reviews of Effects (via Wiley); Cochrane Central Register of Controlled Trials (via Wiley); Health Technology Assessment Database (via Wiley); Web of Science Citation Index Expanded (Clarivate Analytics); Web of Science Conference Proceedings Citation Index (Clarivate Analytics); WHO International Clinical Trials Registry Platform (full search strategy available from Davis *et al* 2018. (5, 9)).The reference lists of systematic reviews and included RCTs were checked to identify any additional trials meeting the inclusion criteria, and bisphosphonate studies were identified from NICE technology appraisal 464.(10)

All records identified by the search were screened by one reviewer, and ten percent screened by a second reviewer. Studies were included if they were randomised controlled trials (RCTs) of adults at risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146.(3) The interventions were DEN, RLX, ROMO, and TPTD compared against each other, the bisphosphonates ALN, RIS, IBN and ZOL, or a non-active treatment. The outcomes were vertebral or hip fractures assessed as either efficacy or safety endpoint, and bone mineral density at the femoral neck (FN BMD). Vertebral fractures could be assessed either radiographically or clinically, and FN BMD was measured by dual energy X-ray absorptiometry (DXA). Where studies planned treatment sequences or open-label extensions with participants in allocated randomised groups, these were included. Studies were excluded if the population was not at risk of osteoporotic fracture, or was a cancer population for which NICE guidelines already exist (11) (12), interventions were not administered in accordance with their licensed indications, insufficient details were reported to allow an assessment of study quality or results, or the RCT was published only in languages other than English. In addition, RCTs of bisphosphonates versus each other or placebo were sought to populate the NMA.

Data relevant to the decision problem were extracted by one reviewer, without blinding to authors or journal, and checked by a second reviewer. Discrepancies were resolved by discussion. Methodological quality of RCTs identified for inclusion was assessed using the Cochrane Collaboration risk of bias assessment criteria. (13)

2.2 Methods for the network meta-analysis

NMAs were conducted, with treatment effects presented as hazard ratios (HR) relative to placebo, for vertebral or hip fractures. A HR less than one reflected a reduced risk of fracture relative to the comparator treatment. For FN BMD, treatment effects are presented as the difference in mean percentage change from baseline in BMD relative to placebo after 1.6 years follow-up (the average duration of follow-up in these studies).

Where studies reported fractures at more than one follow-up point, the longest duration of follow-up was used. To account for different lengths of follow up across the trials, the NMA model assumed an underlying Poisson process for each trial arm, with constant event rate. (14) Both radiologically and clinically assessed vertebral fractures were included in the main analysis. Where a study reported both methods, the radiologically assessed fracture data were used.

Unrelated treatment effects were assumed for all non-bisphosphonate interventions. Exchangeable treatment effects (i.e. a class effect) were assumed for bisphosphonate treatments, whereby individual treatment effects are estimated for each bisphosphonate treatment, but these are assumed to arise from a common distribution (or class), as previously conducted for NICE technology appraisal 464. (10, 15)

Between study heterogeneity for fracture outcomes (i.e. binomial data), as shown by the standard deviation (SD) in treatments effects between studies, was characterised as being mild (SD <0.1) moderate ($0.1 \leq SD < 0.5$), high ($0.5 \leq SD < 1$) or extremely high (≥ 1). Meta-regression was conducted to explore heterogeneity in treatment effects. The node splitting method (16) was used to identify potential inconsistency between direct and indirect evidence.

All analyses were conducted in the freely available software package WinBUGS(17) and R,(18) using the R2Winbugs(19) interface package. Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, as modified by Brooks and Gelman, (20) for two chains with different initial values. For all outcomes, a burn-in of 75,000 iterations of the Markov chain was used with a further 20,000 iterations retained to estimate parameters. Samples from the posterior distributions exhibited moderate correlation between successive iterations of the Markov chain so were thinned by retaining every 15^{th} sample.

The absolute goodness of fit was checked by comparing the total residual deviance to the total number of data points included in an analysis. The deviance information criterion (DIC) provides a relative measure of goodness-of-fit that penalises complexity and was used to compare different models for the same likelihood and data. (21) Lower values of DIC are favourable, suggesting a more parsimonious model.

Results are presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). The probability of each intervention ranking was computed by counting the proportion of iterations of the Markov chain in which each intervention had each rank. The treatment effects of each intervention compared to placebo, together with the median rank and probability of being the highest-ranking treatment, are displayed in forest plots.

In addition to the main analysis, four sensitivity analyses were undertaken for vertebral fracture data. The first explored the impact of fracture assessment method by restricting to fracture data assessed clinically, that is radiologically assessed fracture data were excluded. The second explored the assumption that the fracture event rate in each study arm is constant over time. For this sensitivity analysis, only fracture data reported at 12 months follow-up was included. The third sensitivity analysis excluded RCTs considered at high risk of bias by being open label, terminating early, or requiring estimation of number of events or denominators for a study arm from reported percentages or graphical images. Finally, the effect of prior treatment was considered by excluding RCTs which permitted prior bisphosphonate treatment.

3. Results

3.1 Search results

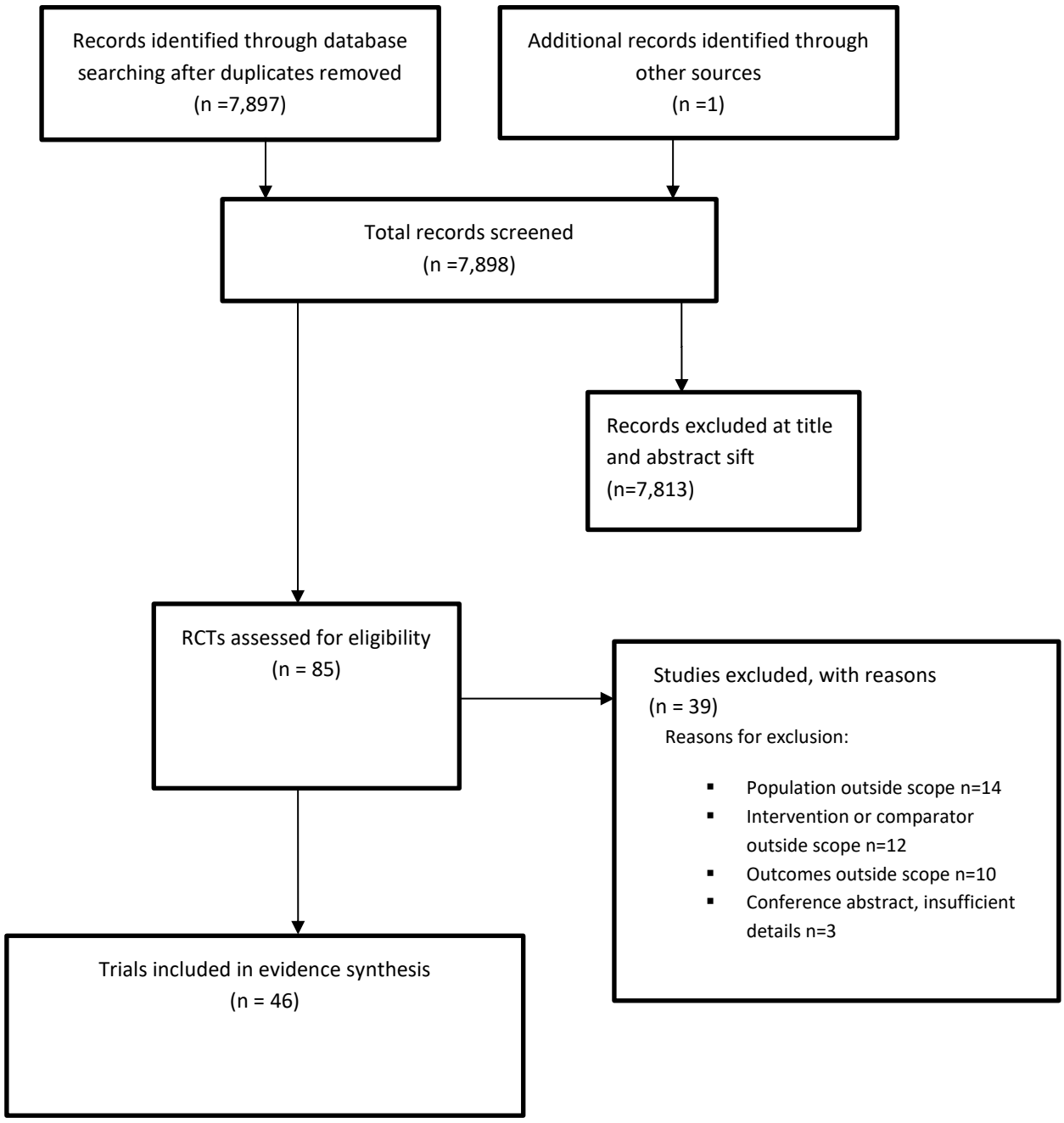
A total of 7,898 citations were identified by the searches. Study selection is shown in Figure 1. At abstract sift, 7,813 were excluded. At full text sift 39 RCTs were excluded (see supplementary material Table S1).

Forty-six RCTs of non-bisphosphonates met the inclusion criteria for the review (shown in supplementary material Table S2). Additionally 49 trials of bisphosphonates were identified that provided data to the NMAs (shown in supplementary material Table S3).

The majority of included trials typically excluded people with underlying conditions that influence bone metabolism, or who were receiving medications that influence bone metabolism. Most studies had a population of women with postmenopausal osteoporosis.

Risk of bias of the non-bisphosphonate trials was assessed by the Cochrane risk of bias tool (Figure S1 in supplementary material). There was unclear reporting of randomisation sequence in 63% included RCTs but low risk of bias for 37% (Figure S1a). Allocation concealment was at low risk of bias in 39% RCTs and unclearly reported in 59% RCTs (Figure S1a). There was a risk of bias from lack of blinding of patients and clinicians in 30% RCTs (Figure S1a). For studies reporting fracture data, outcome assessors were reported as blinded in 53% RCTs; incomplete outcome data, defined as attrition of 10% or more, was reported for 46% of the RCTs. For studies reporting FN BMD data, outcome assessors were reported as blinded in 32% RCTs; incomplete outcome data, defined as attrition of 10% or more, was reported for 55% of the RCTs.

Figure 1 Flow diagram of study selection



3.2 Results of the network meta-analysis

3.2.1.1 Vertebral fracture main analysis

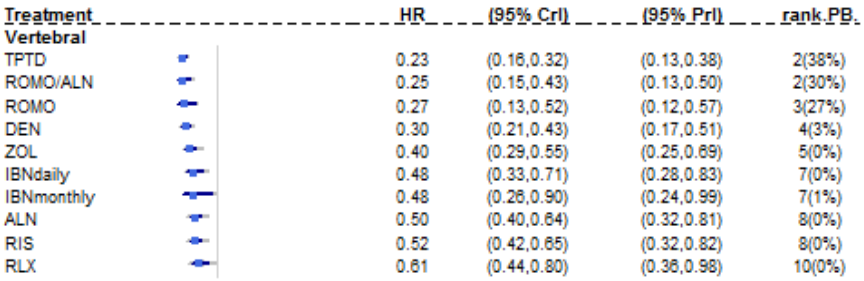
Of the forty-six trials (24 non-bisphosphonate RCTs and 22 bisphosphonate RCTs) included in the vertebral fracture NMA, one RCT was a three arm study(22) whereas all others were two arm studies (shown in supplementary material). The network diagram is shown in supplementary material (Figure S2). There was moderate heterogeneity between studies (supplementary material Table S4).

Figure 2 shows the hazard ratios (HR) of each treatment compared with placebo. The four non-bisphosphonates studied all showed statistically significant benefit relative to placebo: TPTD HR 0.23 (95%CrI 0.16, 0.32); ROMO for one year followed by ALN (ROMO/ALN) 0.25 (95%CrI 0.15, 0.43); DEN HR 0.30 (95%CrI 0.21, 0.43); RLX HR 0.61 (95%CrI 0.44, 0.80). The included bisphosphonate treatments were also associated with statistically significant benefit relative to placebo.

TPTD had the highest probability of being the best treatment (0.38). Pairwise comparisons are shown in supplementary material (Table S5). TPTD was statistically significantly more effective than all active treatments apart from DEN, and ROMO/ALN. TPTD, ROMO/ALN and DEN were all more effective than one or more bisphosphonate (Table S5).

Within the network there were 12 treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency.

Figure 2 Effects of treatment on vertebral fractures relative to placebo



Treatment	HR	(95% CrI)	(95% PrI)	rank.PB.
Vertebral				
TPTD	0.23	(0.16,0.32)	(0.13,0.38)	2(38%)
ROMO/ALN	0.25	(0.15,0.43)	(0.13,0.50)	2(30%)
ROMO	0.27	(0.13,0.52)	(0.12,0.57)	3(27%)
DEN	0.30	(0.21,0.43)	(0.17,0.51)	4(3%)
ZOL	0.40	(0.29,0.55)	(0.25,0.69)	5(0%)
IBNdaily	0.48	(0.33,0.71)	(0.28,0.83)	7(0%)
IBNmonthly	0.48	(0.26,0.90)	(0.24,0.99)	7(1%)
ALN	0.50	(0.40,0.64)	(0.32,0.81)	8(0%)
RIS	0.52	(0.42,0.65)	(0.32,0.82)	8(0%)
RLX	0.61	(0.44,0.80)	(0.36,0.98)	10(0%)

HR=Hazard ratio; CrI=credible interval; PrI=prediction interval; PB=probability of being the best ranking treatment

3.2.1.2 Vertebral fracture sensitivity analyses

The sensitivity analysis which included only fractures as assessed by clinical methods included 20 RCTs.(5) The results were generally consistent with the main analysis, suggesting that treatment effect was not highly influenced by assessment being clinical or radiological. (5)

Twenty-nine RCTs were included in the sensitivity analysis of vertebral fracture data reported at 12 months follow-up. (5) The results were generally consistent with the results of the main analysis, with the exception of the effect shown by RIS. RIS appeared to have a more beneficial treatment effect in the 12 month sensitivity (HR 0.44 95% CrI 0.32-0.60) compared with the main analysis (HR 0.52 95% CrI 0.42-0.65). However, RIS had a zero probability of being the best ranking treatment in both analyses. As the results for the other interventions were generally consistent with the main analysis this sensitivity analysis was considered to support the use of a constant HR across duration of follow-up.

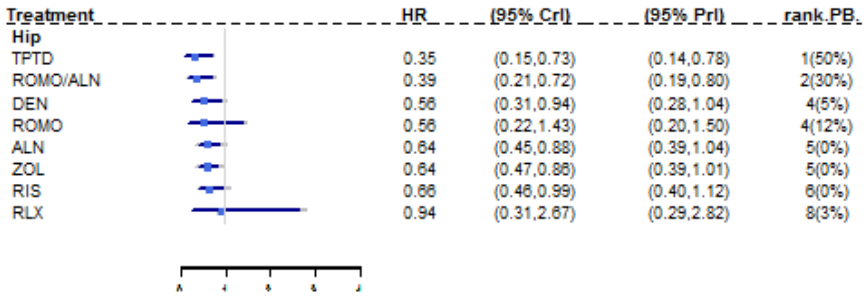
Removing RCTs assessed to have a risk of bias (lack of blinding of patients, physicians or outcome assessors; incomplete reporting of data; or early termination of trial), resulted in a network of 30 RCTs. (5) The results were consistent with the main analysis. (5) Thirty-six RCTs had populations with no prior bisphosphonate treatment. This sensitivity analysis also had results consistent with the main analysis. (5) This suggested that treatment effect was not highly influenced by prior treatment with bisphosphonates.

3.2.2 Hip fractures

Twenty-three RCTs (of which 16 non-bisphosphonate studies and seven bisphosphonate studies) provided hip fracture data to the NMA, with a lower number of fractures than for the vertebral fracture analysis. The network diagram and pairwise comparisons are shown in supplementary material (Figure S2, Table S5). TPTD, ROMO/ALN and DEN were associated with beneficial treatment effects relative to placebo. The comparison to placebo was not statistically significant for RLX. TPTD was associated with the greatest effect, HR 0.35 (95% CrI: 0.15, 0.73), with the highest probability of being the best treatment (0.50), although there was insufficient evidence to differentiate between TPTD and the other active treatments.

Within the network there were 14 treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency. There was moderate heterogeneity between studies (supplementary material Table S4).

Figure 3 Effects of treatment on hip fractures relative to placebo

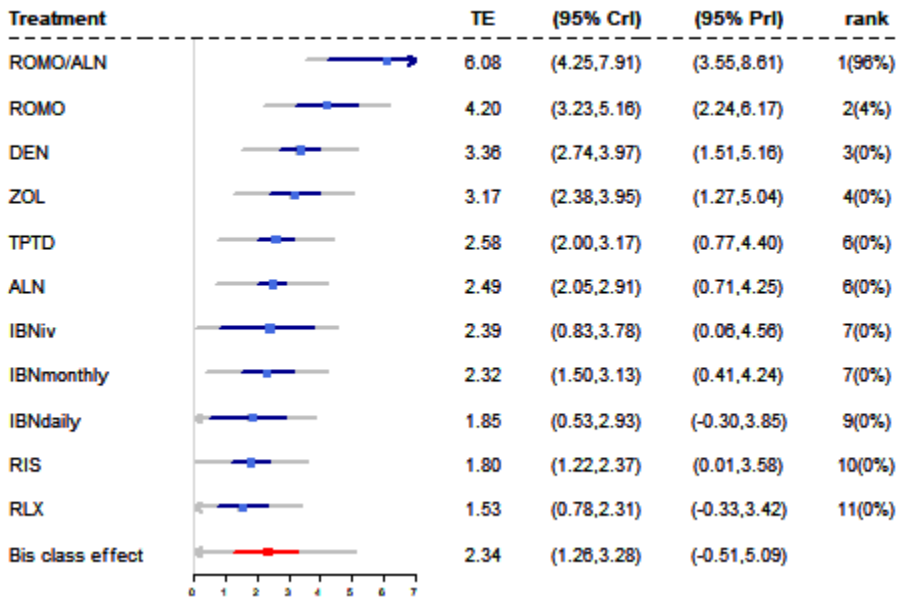


HR=Hazard ratio; CrI=credible interval; PrI=prediction interval; PB=probability of being the best ranking treatment

3.2.3 Femoral neck BMD

Seventy-three RCTs were in the NMA of femoral neck bone mineral density (FN BMD) of which 38 were non-bisphosphonate studies, and 35 were bisphosphonate studies. The network diagram and pairwise comparisons are shown in supplementary material (Figure S2, Table S5). All treatments were associated with statistically significant beneficial treatment effects relative to placebo. ROMO followed by ALN (ROMO/ALN) was associated with the greatest treatment effect, mean difference 6.08 (95% CrI: 4.25, 7.91), with the highest probability of being the best treatment (0.96), and was statistically significantly more effective than all active treatments. There was moderate heterogeneity between studies (supplementary material Table S4).

Figure 4 Effects of treatment on FN BMD relative to placebo



TE= Treatment effect (difference in mean percentage change from baseline in BMD relative to placebo after 1.6 years follow-up); CrI=credible interval; PrI=prediction interval; PB=probability of being the best ranking treatment

There was moderate heterogeneity for all NMAs, however by meta-regression there was no evidence that baseline risk was a significant treatment effect modifier. Meta-regressions were conducted to test for different treatment effects separately according to the mean age of

participants in each study, and the proportion of female participants. There was no evidence that treatment effect varied with age or gender. Results of meta-regressions are available from Davis *et al* 2018. (9)

4. Discussion

A comprehensive search identified forty-six RCTs of DEN, RLX, ROMO and TPTD meeting the review inclusion criteria. Data from these RCTs, and an additional 49 RCTs of ALN, IBN, RIS and ZOL, were synthesised in NMAs. Most of the included RCTs were conducted in postmenopausal women, although there were some trials of men and steroid induced osteoporosis for interventions where these were licensed indications. Adverse event data were reported across RCTs but are not reported here (available in wider review (5)).

All non-bisphosphonates and bisphosphonates studied showed statistically significant benefit relative to placebo in reducing vertebral fractures. This finding complements previous NMAs that have shown benefit on vertebral fracture risk for bisphosphonates, RLX, DEN and TPTD,(15) (23) (24) Unlike other NMAs, this article includes the newer drug ROMO within a NMA against the non-bisphosphonates and bisphosphonates currently recommended for UK treatment. (10) (25) (26) The four non-bisphosphonate interventions studied were all clinically effective for change in FN BMD compared to placebo. Hip fractures were significantly reduced by TPTD, ROMO followed by ALN, and DEN compared to placebo.

The review was limited by being restricted to English language publications, and a lack of study arms to connect the networks meant only one treatment sequence was analysed. Study populations differed according to experience of fracture at baseline, and the review was not designed to address timing of treatment benefit after index fracture. Study populations were not considered separately by gender or age, however meta-regression found no evidence that treatment effect varied with age or gender. Steroid-induced osteoporosis was not considered separately. There was moderate heterogeneity for all NMAs, however by meta-regression there was no evidence that baseline risk was a significant treatment effect modifier. The consistency between direct and indirect evidence was assessed and no strong evidence for inconsistency was found. Studies varied in quality according to blinding and attrition. However, a sensitivity analysis for vertebral fracture rate, removing lower quality studies from the NMA, gave results consistent with the main analysis.

Other sensitivity analyses conducted to assess the impact of assessment method for vertebral fractures (radiographic or clinical), and effect of prior bisphosphonate treatment, demonstrated that the results of the NMA were robust to these potential issues. A sensitivity analysis of duration of study supported the use of a constant HR, to account for differences between trials in follow-up.

In conclusion, TPTD, ROMO followed by ALN, and DEN were all associated with beneficial effects on vertebral and hip fracture risk, and FN BMD, relative to placebo. RLX was associated with beneficial effects on vertebral fracture risk, and FN BMD.

Acknowledgements

Source of funding: This review formed part of a wider review, which was commissioned by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme as project number 14/66/01. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the UK Department of Health. The authors wish to thank Kate Ren for providing feedback on a draft of the article. This review formed part of a wider review, the protocol of which is registered as PROSPERO CRD42018107651.

1. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of World Health Organization study group. 1994. Report No.: WHO Technical Report Series 843.
2. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson AJOI. The Burden of Osteoporotic Fractures: A Method for Setting Intervention Thresholds. 2001;12(5):417-27.
3. National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. Clinical guideline [CG146]2012. Available from: https://www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 [Accessed 20 November 2018].
4. Díez-Pérez A, Marin F, Eriksen EF, Kendler DL, Krege JH, Delgado-Rodríguez M. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: A systematic review and meta-analysis. Bone. 2019;120:1-8.
5. Davis S, Simpson E, Martyn-St James M, Hamilton J, Rawdin A, Wong R, Goka E, Gittoes N, Selby P. A systematic review and economic evaluation of non-bisphosphonates for the prevention of osteoporotic fragility fractures. *Health Technol Assess* (in press).
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009;339.
7. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Annals of Internal Medicine. 2015;162(11):777-84.
8. Food and Drug Administration FDA Label Evenity 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761062s000lbl.pdf. [Accessed 14 August 2019].
9. Davis S, Simpson EL, Martyn-St James M, Hamilton J, Rawdin A, Wong R, et al. A systematic review and economic evaluation of non-bisphosphonates for the prevention of osteoporotic fragility fractures (ID901). School of Health and Related Research (ScHARR), University of Sheffield, 2018. https://www.nice.org.uk/guidance/gid-ta10072/documents/assessment-report. [Accessed 14 August 2019].
10. National Institute for Health and Clinical Excellence. Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161). London: National Institute for Health and Clinical Excellence (NICE); 2015. This report was commissioned by the NIHR HTA Programme as project number 13/04/001.
11. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management. NICE guideline [NG101]2018. Available from: https://www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 [Accessed 20 November 2018].
12. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management. clinical guideline [CG175]2014. Available from: https://www.nice.org.uk/guidance/cg146/resources/osteoporosis-assessing-the-risk-of-fragility-fracture-pdf-35109574194373 [Accessed 20 November 2018].
13. Higgins J, Altman A, Sterne J, on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Churchill R, Chandler J, Cumpston M, editors. Cochrane Handbook for Systematic Reviews of Interventions version 520 (updated June 2017): Cochrane, 2017. Available from www.training.cochrane.org/handbook; 2017. [Accessed 14 August 2019].

14. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.
15. Sanderson J, Martyn-St James M, Stevens J, Goka E, Wong R, Campbell F, et al. Clinical effectiveness of bisphosphonates for the prevention of fragility fractures: A systematic review and network meta-analysis. Bone. 2016;89:52-8.
16. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7-8):932-44.
17. Lunn DJ, Thomas A, Best N, Spiegelhalter DJS, Computing. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. 2000;10(4):325-37.
18. R CORE TEAM. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. 2017.
19. Sturtz S., Ligges U., A. G. R2WinBUGS: A package for running WinBUGS from R. Journal of Statistical Software. 2005;12:1-16.
20. Brooks S. P., A. G. General methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics. 1998;7:434-55.
21. Spiegelhalter DJ, Best NG, Carlin BR, Van Der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society Series B-Statistical Methodology. 2002;64:583-616.
22. Muscoso E, Puglisi N, Mamazza C, Lo Giudice F, Testai M, Abbate S, et al. Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. Eur Rev Med Pharmacol Sci. 2004;8(2):97-102.
23. Liu GF, Wang ZQ, Liu L, Zhang BT, Miao YY, Yu SN. A network meta-analysis on the short-term efficacy and adverse events of different anti-osteoporosis drugs for the treatment of postmenopausal osteoporosis. Journal of Cellular Biochemistry. 2018;119(6):4469-81.
24. Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, et al. Comparative Effectiveness of Drug Treatments to Prevent Fragility Fractures: A Systematic Review and Network Meta-Analysis. Journal of Clinical Endocrinology & Metabolism. 2012;97(6):1871-80.
25. National Institute for Health and Care Excellence. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Technology appraisal guidance [TA204]. London: NICE.2010 [Available from: https://www.nice.org.uk/guidance/ta70 [Accessed 31 October 2018].
26. National Institute of Heath and Care Excellence (NICE). Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women [TA161] 2008 [Available from: https://www.nice.org.uk/Guidance/TA161 [Accessed 2 November 2018].

Funding Source

Source of funding: This review formed part of a wider review, which was commissioned by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme as project number 14/66/01. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the UK Department of Health. This review formed part of a wider review, the protocol of which is registered as PROSPERO CRD42018107651.