The efficacy and safety of vertebral fracture prevention therapies in post-menopausal osteoporosis treatment

WHICH THERAPIES WORK BEST? A NETWORK META-ANALYSIS

Objectives
Osteoporosis has become an increasing concern for older people as it may potentially lead to osteoporotic fractures. This study is designed to assess the efficacy and safety of ten therapies for post-menopausal women using network meta-analysis.

Methods
We conducted a systematic search in several databases, including PubMed and Embase. A random-effects model was employed and results were assessed by the odds ratio (OR) and corresponding 95% confidence intervals (CI). Furthermore, with respect to each outcome, each intervention was ranked according to the surface under the cumulative ranking curve (SUCRA) value.

Results
With respect to preventing new vertebral fractures (nVF), all ten drugs outperformed placebo, and etidronate proved to be the most effective treatment (OR 0.24, 95% CI 0.14 to 0.39). In addition, zoledronic acid and parathyroid hormone ranked higher compared with the other drugs. With respect to preventing clinical vertebral fractures (CVF), zoledronic acid proved to be the most effective drug (OR = 0.25, 95% CI 0.08 to 0.92), with denosumab as a desirable second option (OR = 0.48, 95% CI 0.22 to 0.96), when both were compared with placebo. As for adverse events (AE) and severe adverse events (SAE), no significant difference was observed. According to SUCRA, etidronate ranked first in preventing CVF; parathyroid hormone and zoledronic acid ranked highly in preventing NFV and CVF. Raloxifene was safe with a high rank in preventing AEs and SAEs though performed unsatisfactorily in efficacy.

Conclusions
This study suggests that, taking efficacy and safety into account, parathyroid hormone and zoledronic acid had the highest probability of satisfactory performance in preventing osteoporotic fractures.

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Keywords: Post-menopausal osteoporosis, Vertebral fracture, Prevention, Network meta-analysis

Article focus
- This study is designed to assess the efficacy and safety in the prevention of vertebral fractures of ten therapies for post-menopausal osteoporosis using network meta-analysis.

Key messages
- Parathyroid hormone and zoledronic acid might have the highest probability of satisfactory performance in prevention of vertebral fractures in post-menopausal osteoporosis.

Strengths and limitations
- Our study fills the void of existing research and most of our results fall in line with existing clinical studies and may have promising potential clinical implications. However, one limitation of our study is the small number of relevant studies available for reference and some...
key comparisons were missing in the analysis of CVF and SAE.

Introduction

Osteoporosis has become an increasing concern for the older population. It is a disease characterised by decreased bone strength and may lead to osteoporotic fractures. It may also significantly affect health and quality of life, and create a heavy burden for both families and society in general. A previous study demonstrated that the annual incidence rate of fractures increases with age, especially among post-menopausal women who are more vulnerable to osteoporosis due to oestrogen deficiency. According to a survey, about 1.5 million fragility fractures are attributed to osteoporosis every year in the United States, and about half of these are vertebral fractures (VF). Patients with a previous VF have a higher risk of a second VF within the next year. Therefore, the primary goal of osteoporosis treatment is to reduce the incidence rate of new vertebral fractures (NVF).

Several therapies are currently available for the prevention and treatment of post-menopausal osteoporosis (PMO) including oral bisphosphonates (e.g. alendronate, (ALE)), oestrogen replacement therapy, selective oestrogen receptor modulator (e.g. risedronate (RIS)), and calcitonin and biological agents (e.g. denosumab (DEN)). However, the long-term use of oestrogen replacement therapy significantly increases the risk of breast and ovarian cancer, and calcitonin is not widely used in clinical management. Therefore, these two therapies were not included in this study.

Oral bisphosphonates are the most common treatment for osteoporosis. In the United Kingdom, about 10% of women aged 70 years or above were treated with bisphosphonates in 2005. The National Osteoporosis Guideline Group and the National Institute for Clinical Excellence, both in the United Kingdom, recommend ALE as the first choice of therapy for reducing fracture risk. Ibandronate (IBA) and RIS are recommended as secondary options. In addition, clodronate (COL) has demonstrated its anti-resorptive efficacy in various other diseases related to the increased resorption of bone and the prevention of PMO. Etidronate (ETI), a first-generation bisphosphonate which inhibits resorption, has the potential to inhibit mineralisation and cause osteomalacia. Studies on the long-term use of ALE have shown that it retains the benefit of successfully reducing bone loss and VF. Additionally, strontium ranelate (STR) is another anti-osteoporotic agent which can stimulate bone formation and reduce resorption. DEN is a potent agent which can reduce the risk of NVF by increasing bone density. Raloxifene (RAL) increases bone mineral density in the spine and femoral neck and reduces risk of vertebral fracture. The beneficial effects of parathyroid hormone (PTH) treatment have also been clearly demonstrated through randomised clinical trials (RCT) and its few adverse events (AE) make it a good candidate for various uses such as PTH treatment, leading to induction bone formation without inducing bone resorption.

There have been many RCTs conducted on these therapies in order to identify the most effective method in preventing NVF in post-menopausal women. Several studies attempting to compare the results of pairwise meta-analyses in regard to the prevention and safety of different treatments can also be found in the current literature. However, it is still difficult to reach a conclusion due to the limitations of the traditional pairwise meta-analysis (i.e. there is no concise synthesis of the data). Furthermore, the reduction of fracture risk is mainly demonstrated in placebo-controlled trials, and head-to-head comparisons of different agents are rare.

A network meta-analysis (NMA) can estimate the differences in efficacy and safety of various treatments. This can provide relevant comparative evidence that compares all treatments by linking the treatments in a network of trials. The main objective of this study was to assess the efficacy and safety of ten commonly used therapies to determine the optimal treatment for post-menopausal women who are at risk for VF (available agents include ALE, COL, DEN, ETI, IBA, PTH, RAL, RIS, STR and zoledronic acid (ZOL)).

Materials and Methods

Data search strategy. Our research began with a systematic search of several databases including PubMed and Embase, as well as the Cochrane library, ClinicalTrials.gov, CNKI, and Wanfang databases. The search only included papers written in English. The keywords for the search included: “post-menopausal osteoporosis”, “randomised clinical trials”, “alendronate”, “raloxifene”, “denosumab”, “parathyroid hormone”, “ibandronate”, “risedronate”, “clodronate”, “etidronate”, “zoledronic acid” and “strontium ranelate”. More details can be seen in supplementary Table i.

In order to ensure the high quality of selection and accuracy in our study, two reviewers independently identified the title and abstract of each eligible paper. Only papers whose title and abstract fit the inclusion criteria passed the initial screening. After initial filtering, the full texts of remaining papers were further examined. Studies with insufficient information, irrelevant outcomes or lack of comparison with other interventions were removed. Any disagreement was resolved through discussion until consensus was reached.

Inclusion and exclusion criteria. Studies were included in the network meta-analysis if they met all of the following criteria: 1) the study was designed as an RCT; 2) subjects were post-menopausal women with osteoporosis; 3) the study was designed to compare the effects...
of the following drugs with placebo (PLA) or between each other: ALE, COL, DEN, ETI, IBA, PTH, RAL, RIS, STR, and ZOL; 4) at least one of the following outcomes was included as the primary or secondary endpoint: NVF; clinical vertebral fractures (CVF); AEs and serious adverse events (SAE). Studies were excluded if: 1) not all women involved in the study were post-menopausal; 2) men were included in the study and could not be separated from women; 3) the treatment contained drugs that were not mentioned above and could not be separated.

**Data extraction and statistical analysis.** The full text of each identified study was then further evaluated. The treatment data, consisting of dosing regimen, treatment duration, blinding condition, trial size and outcomes of the study, were extracted; patients’ mean age, and year of menopause were also collected. Firstly, a meta-analysis with a random-effects model was performed to compare different interventions with PLA directly by R Software (Version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria). The inter-group discrepancies were assessed by odds ratio (OR) with a corresponding 95% confidence interval (CI). Heterogeneity was assessed using Cochrane’s Q test and the chi-squared test. Heterogeneity across the studies was considered to be significant if \( p < 0.05 \) for the Q test or chi-squared > 50%. We then used a fixed-effects model (Mantel-Haenszel method)\(^{21}\) and a random-effects model (DerSimonian-Laird method)\(^{22}\) to minimise the effect of heterogeneity. Moreover, one-way sensitivity analysis was also used to evaluate the robustness of the results.

In addition, a NMA combining direct and indirect results was carried out in R Software (Version 3.2.3). The results were demonstrated by cumulative OR and corresponding 95% CI, which represents the interval in the domain of a posterior probability distribution.\(^{23}\) As shown in Spiegelhalter et al.,\(^{24}\) we employed a random-effects model within a Bayesian framework, and a mesh-like diagram was drawn based on incorporated studies. Meanwhile, we performed a probabilistic analysis to give a probable ranking for each intervention, which was weighted by the SUCRA.\(^{25}\) The sum of the ranking possibility of each treatment is the SUCRA. The higher the SUCRA of a given treatment, the more efficient or safe it is.

**Results**

**Study characteristics.** The drugs involved in our study include PLA, ALE, COL, DEN, ETI, IBA, PTH, RAL, RIS, STR, and ZOL, and the endpoints include NVF, CVF, AE and SAE. Here, NVF was defined as a reduction of \( \geq 20\% \), with an absolute decrease of \( \geq 4 \) mm, in the height of any vertebral body between baseline and the end of treatment, and it was determined as our primary outcome because it occurred the most frequently in the included studies. CVF was defined as new or worsening back pain with a reduction in vertebral body height of 20% (grade 1) or more, as compared with baseline radiographs, or a reduction in vertebral body height of 25% (grade 2) or more if no baseline radiograph was available. Gastrointestinal events, hypocalcaemia, bacterial cellulitis, eczema, hypersensitivity, cardiac disorders and vascular disorders were considered as AEs of interest. A total of 1609 records were initially included in this study (Fig. 1). After removing duplicates and screening by scanning abstracts and titles, 70 studies remained. Subsequent to further
exclusion, 42 studies met the criteria and were finally included in our study. Among the 42 studies, shown in Figure 2, most of the direct comparisons are between Pla and other drugs. Furthermore, Den and Ale appeared the most frequently, as illustrated in Table I. In total, 92,904 post-menopausal women with osteoporosis were involved in our study. Most of the studies were classified as double-blind with the remaining being assessor blind, open label or unknown.

**NVF.** As shown in Figure 3, we found that all ten therapies were more effective than placebo in terms of NVF. Specifically, among the ten therapies, EtI outperformed Ale, COL, IBA, RAL, RIS, STR and ZOL. ZOL performed better than Ale, IBA, RAL, RIS and STR, and PTH achieved
| Comparison study information | Study duration (yrs) | Blinding | Mean age (yrs) | Time after menopause (yrs) | Treatment | Regimen dosing* | Patients (n) | Outcome† |
|-----------------------------|---------------------|----------|---------------|--------------------------|-----------|----------------|-------------|----------|
| ALE vs PLA                  | 10                  | √        | 64/64         | 16/17                    | ALE/PLA   | 5, 10, or 20 mg QD | 994         | 1, 4     |
| Bone et al19                | 2                   | √        | 71.1/71.1     | 24.2/22.8                | ALE/PLA   | 1, 2.5, or 5 mg QD | 359         | 1, 3, 4  |
| Black et al11               | 3                   | √        | 71/70.7       | NS                       | ALE/PLA   | 5 to 10 mg QD    | 2027        | 1, 2, 4  |
| Cummings et al13           | 4.2                 | √        | 67.7/67.6     | NS                       | ALE/PLA   | 5 to 10 mg QD    | 4432        | 1        |
| Saag et al12               | 0.92                | √        | NS            | NS                       | ALE/PLA   | 5 mg QD          | 150         | 1        |
| Adachi et al41             | 2                   | √        | NS            | NS                       | ALE/PLA   | 5 mg QD          | 54          | 1        |
| COL vs PLA                  | McCloskey et al42   | 3        | 67.5/67.7     | NS                       | COL/PLA   | 800 mg QD        | 593         | 1        |
| Cummings et al13           | 3                   | √        | 73.2/72.3     | NS                       | COL/PLA   | 800 mg QD        | 5592        | 1, 3, 4  |
| Grant et al26              | 3                   | √        | NS            | NS                       | COL/PLA   | 60 mg Q6M        | 3420        | 1, 3, 4  |
| Bone et al11               | 3                   | √        | 71.9/71.8     | 23.7/23.7                | COL/PLA   | 60 mg Q6M/60 mg Q6M | 9100       | 2, 3, 4  |
| Eti vs PLA                  | Lyritis et al57     | 16       | Open label    | 25.1/26.4                | Eti/PLA   | 400 mg QD        | 100         | 1        |
| Montessori et al44         | 1                   | √        | 62.1/62.9     | 3.4/3.5                  | Eti/PLA   | 400 mg QD        | 71          | 1, 4     |
| Adachi et al60             | 1                   | √        | NS            | NS                       | Eti/PLA   | 400 mg QD        | 70          | 1, 4     |
| Storm et al63              | √                    | 67.8/68.9 | 21.2/21.9     | Eti (Cyclic)/PLA         | 400 mg QD | 66         | 1          |
| Shiota et al45             | NS                  | 60.7/62.7 | 13.8/15.3     | Eti (Cyclic)/PLA         | 200 mg QD | 40          | 1          |
| IBA vs PLA                  | Chesnut et al36     | 3        | 69/69         | 20.9/20.8                | IBA/PLA   | 2.5 mg QD, or 20 mg QOD | 2946       | 1, 2, 3, 4 |
| Chesnut et al36            | 3                   | √        | 68.7/68.8     | 20.8/20.8                | IBA/PLA   | 2.5 mg QD, or 20 um QZD | 2929       | 1, 2, 3, 4 |
| PTH vs PLA                  | Neer et al16        | 1.75     | 70/69         | NS                       | PTH/PLA   | 20, 40 mcg QD    | 1637        | 1        |
| Greenspan 200718            | 1.5                 | √        | NS            | NS                       | PTH/PLA   | 100 ug QD        | 471         | 2        |
| RAL vs PLA                  | Lutfi et al54       | 1        | 69.9/68.2     | 22/22.2                  | RAL/PLA   | 60, or 120 mg QD | 143         | 1        |
| Ettinger et al14           | 4                   | √        | 65/65         | 17-21/18-21              | RAL/PLA   | 60, or 120 mg QD | 6828        | 1        |
| Mori et al14               | 1                   | √        | 65.2/64.7     | 15.2/15.8                | RAL/PLA   | 60 mg QD/       | 202         | 1, 3, 4  |
| 120 mg QD                  |                      |           |               |                          |           | 1, 3, 4         |             |          |
| Ensrud et al54             | 5.6                 | √        | 67.5/67.5     | NS                       | RAL/PLA   | 60 mg QD        | 10101       | 1        |
| RIS vs PLA                  | Fogelman et al10     | 2        | 65/64         | 18/17                    | RIS/PLA   | 2.5, or 5 mg QD  | 543         | 1, 3, 4  |
| Hooper et al10             | √                    | 53/52.6   | 46.1w/46.6w   | RIS/PLA                 | 2.5, or 5 mg QD | 383       | 1, 3, 4  |
| Palomba et al18            | 1                   | √        | 52.3/51.4     | 16.4w/17.5w              | RIS/PLA   | 35 mg QW        | 81          | 1        |
| Register et al49           | √                    | 71/71     | 24/25         | RIS/PLA                 | 2.5, or 5 mg QD | 1226      | 1, 3, 4  |
| Harris et al51             | √                    | 69/68     | 24/24         | RIS/PLA                 | 5 mg QD   | 1641         | 1, 3, 4  |
| Wallach et al48            | √                    | 64.3/64.2 | NS            | RIS/PLA                 | 5, or 10 mg QD | 255       | 1        |
| Morteisen et al54          | √                    | 52.1/51.3 | 3             | RIS/PLA                 | 5 mg QD   | 111          | 1         |
| Clemmensen et al48         | √                    | 68/70     | 18            | RIS/PLA                 | 2.5 mg QD | 132          | 1         |
| STR vs PLA                  | Meunier et al42     | 3        | 69.2/69.4     | 21.6/22.1                | PLA/STR   | 2 g QD         | 1649       | 1, 4     |
| Register et al12           | 5                   | √        | 76.8/76.7     | 28.4/28.5                | PLA/STR   | 2 g QD         | 5091       | 1, 3, 4  |
| ZOL vs PLA                  | Black et al17       | 3        | 73.1/73       | NS                       | ZOL/PLA   | 5 mg QY        | 7765       | 1, 2, 3, 4 |
| Black et al17              | 3                   | √        | 78/78.1       | NS                       | ZOL/PLA   | 5 mg QY        | 190         | 1, 4     |
| Popp et al18               | 3                   | √        | 76.5/77       | NS                       | ZOL/PLA   | 5 mg QY        | 110         | 1, 3, 4  |
| RAL vs ALE                  | Recker et al4       | √                    | 65.5/65.7     | 18.5/19                  | RAL/ALE   | 60 mg QD/10 mg QD | 1423       | 1, 2, 4  |
| Iwamoto et al13            | 1                   | √                    | 70.3/68.5     | NS                       | RAL/ALE   | 60 mg QD/5 mg QD | 122         | 1, 4     |
| RIS vs ALE                  | Thomas et al19      | 1.25      | NS            | 75/76                    | RIS/ALE   | 60 mg QD        | 11007       | 1        |
| RIS vs Eti                  | Fukunaga19          | √                    | 63.1/62.1     | 13.8/12.8                | RIS/Eti (Cyclic) | 2.5 mg QD/200 mg QD | 209       | 1, 4     |
| DEN vs IBA                  | Recknor et al46     | 1         | 67.2/66.2     | 20.4/19.7                | DEN/IBA   | 60 mg Q6M       | 833         | 1, 4     |

*Regimen dosing: QD, once a day; QW, once a week; QM, once a month; QY, once a year; IU, International Unit
†Outcome 1, New vertebral fractures; 2, Clinical vertebral fractures; 3, Serious adverse events; 4, Adverse events. Ns, not specified
ALE, alendronate; PLA, placebo; COL, clodronate; DEN, denosumab; Eti, eronate; IBA, ibandronate; PTH, parathyroid hormone; RAL, raloxifene; RIS, risedronate; STR, strontium ranelate; ZOL, zoledronic acid
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**Comparisons between direct and indirect evidence.** The node-splitting method (a method comparing direct and indirect evidence for a particular comparison of treatments) and Bayesian p-values were used to report inconsistencies between direct comparison and indirect comparison of our results (Fig. 7). The overall consistency condition was satisfactory except for the outcome of AEs. Within AEs, inconsistency existed in the comparisons between DEN and PLA, IBA and PLA, and IBA and DEN, with corresponding p values of 0.028, 0.026 and 0.026, respectively.

**Relative ranking of ten interventions.** In this section, we employed SUCRA to give a probability rank for ten interventions. The results were shown in Figure 8 and Table II. From these results, the following conclusions could be made: in terms of the primary outcome of NVF,
Fig. 4
Forest plot of clinical vertebral fractures (COL, clodronate; PTH, parathyroid hormone; ZOL, zoledronic acid; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; ALE, alendronate; PLA: placebo).

Fig. 5
Forest plot of adverse events (ETI, etonate; COL, clodronate; ZOL, zoledronic acid; STR, strontium ranelate; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; RIS, risedronate; ALE, alendronate; PLA: placebo).
ETI was the best intervention due to its top probability ranking, followed sequentially by ZOL and PTH. With respect to CVF, ZOL ranked top, followed by DEN. In terms of AEs and SAEs, the performance of these interventions was hard to distinguish except for RAL, which indicated that most therapies were less likely to cause AEs and SAEs.

**Discussion**

This study compared the efficacy and safety of ten common prevention therapies for PMO treatment (ALE, COL, DEN, ETI, IBA, PTH, RAL, RIS, STR and ZOL). NFV was the primary endpoint; CVF, AEs and SAEs were the secondary endpoints. A NMA was performed to measure the efficacy and safety of these prevention therapies, in which 42 academic papers were involved, and provided head-to-head comparisons of different interventions.

The NMA results showed that all ten therapies were notably more effective than PLA in the prevention of NFV. ETI ranked first with a SUCRA value of 0.916, followed by PTH and ZOL. Furthermore, ZOL and DEN worked most efficiently in reducing the risk of CVF while the data reporting ETI in preventing CVF were not available in our study. In view of statistical insignificance, none of the therapies (PLA included) exhibited much difference in triggering AEs and SAEs. Moreover, the rank possibility of SUCRA of both NFV and CVF suggested that ZOL and PTH were recommended for clinical treatment because they ranked higher in the primary efficacy measurement. Even though ETI performed the best in NFV, its data about CVF were missing so we were unable to draw a conclusion about its efficacy.

Our results were in accordance with the mixed treatment comparison of bisphosphonate therapies undertaken by Jansen et al, which drew conclusions from seven RCTs and suggested that ZOL had a 98% probability of reducing the risk of NFV and was more effective than ALE, IBA and RIS. A meta-analysis performed by Cranney et al indicated that one to three years of ETI treatment increased bone density by 4.06% in the lumbar spine (95% CI 3.12 to 5.00), which was also consistent with our results.

According to the results, DEN worked well in preventing NFV and presented no statistical difference in AEs and SAEs. This was in accordance with previous studies. However, a meta-analysis consisting of approximately nine RCTs and 10,329 participants performed by Anastasilakis et al indicated that DEN caused a statistically insignificant reduction in fracture risk (OR = 0.74, 95% CI 0.33 to 1.64, p = 0.450) and an increased risk of SAEs (OR = 1.83, 95% CI 1.10 to 3.04, p = 0.020) and serious infections (OR = 4.45, 95% CI 1.15 to 17.14, p = 0.030). These results cast doubt on the safety of DEN. Nevertheless, due to a larger sample size and extensive
### New vertebral fractures

| Study         | P-value | OR (95% CI)          |
|---------------|---------|----------------------|
| **ALE vs PLA**|         |                      |
| direct        | 0.50    | (0.40, 0.63)         |
| indirect      | 0.32    | (0.24, 0.41)         |
| network       | 0.30    | (0.22, 0.39)         |
| **DEN vs PLA**|         |                      |
| direct        | 0.31    | (0.22, 0.42)         |
| indirect      | 0.34    | (0.049, 5.1)         |
| network       | 0.31    | (0.23, 0.44)         |
| **ETI vs PLA**|         |                      |
| direct        | 0.20    | (0.092, 0.38)        |
| indirect      | 0.92    | (0.088, 26)          |
| network       | 0.21    | (0.12, 0.46)         |
| **IBA vs PLA**|         |                      |
| direct        | 0.49    | (0.37, 0.64)         |
| indirect      | 0.29    | (0.037, 2.5)         |
| network       | 0.49    | (0.37, 0.62)         |
| **RAL vs PLA**|         |                      |
| direct        | 0.59    | (0.47, 0.76)         |
| indirect      | 0.38    | (0.16, 0.88)         |
| network       | 0.57    | (0.46, 0.71)         |
| **RIS vs PLA**|         |                      |
| direct        | 0.47    | (0.37, 0.61)         |
| indirect      | 0.52    | (0.31, 0.85)         |
| network       | 0.48    | (0.39, 0.60)         |
| **RAL vs ALE**|         |                      |
| direct        | 0.70    | (0.34, 1.5)          |
| indirect      | 1.2     | (0.90, 1.7)          |
| network       | 1.1     | (0.86, 1.5)          |
| **RIS vs ALE**|         |                      |
| direct        | 1.1     | (0.67, 1.6)          |
| indirect      | 0.91    | (0.63, 1.2)          |
| network       | 0.96    | (0.74, 1.2)          |
| **IBA vs DEN**|         |                      |
| direct        | 0.95    | (0.11, 7.4)          |
| indirect      | 1.6     | (1.0, 2.4)           |
| network       | 1.6     | (1.0, 2.4)           |
| **RIS vs ETI**|         |                      |
| direct        | 0.34    | (0.014, 5.0)         |
| indirect      | 2.6     | (1.3, 5.5)           |
| network       | 2.2     | (1.0, 4.3)           |

### Adverse events

| Study         | P-value | OR (95% CI)          |
|---------------|---------|----------------------|
| **ALE vs PLA**|         |                      |
| direct        | 0.88    | (0.64, 1.2)          |
| indirect      | 1.3     | (0.60, 2.8)          |
| network       | 0.92    | (0.69, 1.2)          |
| **DEN vs PLA**|         |                      |
| direct        | 0.84    | (0.70, 1.0)          |
| indirect      | 1.6     | (0.96, 2.6)          |
| network       | 0.93    | (0.76, 1.2)          |
| **ETI vs PLA**|         |                      |
| direct        | 1.3     | (0.48, 3.3)          |
| indirect      | 1.1     | (0.47, 2.6)          |
| network       | 1.2     | (0.63, 2.3)          |
| **IBA vs PLA**|         |                      |
| direct        | 1.4     | (1.0, 1.8)           |
| indirect      | 0.73    | (0.46, 1.1)          |
| network       | 1.2     | (0.89, 1.5)          |
| **RAL vs PLA**|         |                      |
| direct        | 1.2     | (0.64, 2.3)          |
| indirect      | 0.85    | (0.48, 1.4)          |
| network       | 0.97    | (0.63, 1.4)          |
| **RIS vs PLA**|         |                      |
| direct        | 1.2     | (0.82, 1.7)          |
| indirect      | 1.3     | (0.40, 4.2)          |
| network       | 1.2     | (0.83, 1.6)          |
| **RAL vs ALE**|         |                      |
| direct        | 0.95    | (0.62, 1.4)          |
| indirect      | 1.4     | (0.64, 2.8)          |
| network       | 1.0     | (0.72, 1.5)          |
| **IBA vs DEN**|         |                      |
| direct        | 0.87    | (0.58, 1.3)          |
| indirect      | 1.6     | (1.2, 2.3)           |
| network       | 1.2     | (0.90, 1.7)          |
| **RIS vs ETI**|         |                      |
| direct        | 1.0     | (0.48, 2.2)          |
| indirect      | 0.93    | (0.34, 2.7)          |
| network       | 0.99    | (0.53, 1.8)          |

### Clinical vertebral fractures

| Study         | P-value | OR (95% CI)          |
|---------------|---------|----------------------|
| **ALE vs PLA**|         |                      |
| direct        | 0.44    | (0.10, 2.1)          |
| indirect      | 2.5     | (0.13, 92.3)         |
| network       | 0.35    | (0.16, 2.4)          |
| **RAL vs PLA**|         |                      |
| direct        | 0.66    | (0.17, 2.8)          |
| indirect      | 0.11    | (0.0016, 2.5)        |
| network       | 0.54    | (0.13, 1.7)          |
| **RAL vs ALE**|         |                      |
| direct        | 0.26    | (0.0080, 3.5)        |
| indirect      | 1.6     | (0.19, 12.2)         |
| network       | 0.97    | (0.16, 3.6)          |

### Serious adverse events

| Study         | P-value | OR (95% CI)          |
|---------------|---------|----------------------|
| **DEN vs PLA**|         |                      |
| direct        | 1.2     | (0.90, 1.5)          |
| indirect      | 2.3     | (1.0, 4.8)           |
| network       | 1.2     | (0.95, 1.6)          |
| **IBA vs PLA**|         |                      |
| direct        | 1.2     | (0.82, 1.7)          |
| indirect      | 0.63    | (0.29, 1.3)          |
| network       | 1.1     | (0.71, 1.5)          |
| **IBA vs DEN**|         |                      |
| direct        | 0.54    | (0.27, 1.1)          |
| indirect      | 1.0     | (0.65, 1.6)          |
| network       | 0.88    | (0.55, 1.2)          |

Node-splitting results for new vertebral fractures, clinical vertebral fractures, adverse events and serious adverse events (ETI, eronate; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; RIS, risedronate; ALE, alendronate; PLA, placebo).
comparisons of our studies, the confidence intervals presented in our study are relatively narrow, thus our results were more reliable. However, in a practical clinical environment, the patient’s adverse reactions should still be regularly monitored to improve medication safety.

One limitation of our study in the analysis of CVF and SAE, was the number of relevant studies being relatively small and some key comparisons were missing, meaning that most evidence came from indirect comparisons instead of direct comparisons. Consequently, the results of CVF and SAE should be interpreted with caution. Furthermore, the OR of RIS and ETI in preventing NVF contained a significant contradiction (direct: 0.34, indirect: 2.6) because all of the direct evidence comes from a single RCT performed by Fukunaga,19 which only involved 209 participants. In addition, the endpoint discontinuation should be taken into account. For example, ZOL is the only therapy administered to patients intravenously on a yearly basis, which means greater compliance of patients.67,68 This discrepancy led to an

| Outcome | PLA | ALE | COL | DEN | ETI | IBA | PTH | RAL | RIS | STR | ZOL |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| NVF     | 0.001 | 0.402 | 0.439 | 0.785 | 0.916 | 0.427 | 0.813 | 0.285 | 0.450 | 0.113 | 0.85 |
| CVF     | 0.119 | 0.473 | 0.349 | 0.576 | -   | 0.534 | 0.584 | 0.507 | -   | -   | 0.854 |
| AEs     | 0.654 | 0.756 | 0.227 | 0.772 | 0.409 | 0.398 | -   | 0.686 | 0.374 | 0.528 | 0.193 |
| SAEs    | 0.510 | 0.381 | 0.529 | 0.185 | -   | 0.411 | -   | 0.816 | 0.624 | 0.444 | 0.585 |

PLA, placebo; ALE, alendronate; COL, clodronate; DEN, denosumab; ETI, eronate; IBA, ibandronate; PTH, parathyroid hormone; RAL, raloxifene; RIS, risendronate; STR, strontium ranelate; ZOL, zoledronic acid; NVF, new vertebral fractures; CVF, clinical vertebral fractures; AEs, adverse events; SAEs, serious adverse events
assumption that the significant performance of ZOL was partly attributed to the patient’s compliance. Despite the limitations above, our study fills the void in existing research, and most of our results fall in line with existing clinical studies and may have promising potential clinical implications.

In conclusion, this study suggests that PTH and ZOL have the highest probability of treatment efficacy. In view of the limitations above, we expect more clinical trials on PMO to be performed in order to continue closing the existing gaps in knowledge.

Supplementary material

Tables showing the search strategy and the efficacy and safety of agents for post-menopausal osteoporosis according to the network meta-analysis are available alongside this article online at www.bjrn.boneandjoint.org.uk

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