BJR

RESEARCH

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

WHICH THERAPIES WORK BEST? A NETWORK META-ANALYSIS

G. Wang,*
L. Sui,*
P. Gai,
G. Li,
X. Qi,
X. Jiang

The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Shangdong, China

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 NVF 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.

Cite this article: *Bone Joint Res* 2017;6:452–463.

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

- G. Wang, MD, Associate Chief Physician,
- L. Sui, MD, Attending Physician,
- P. Gai, MD, Attending Physician,
- G. Li, MD, Attending Physician,
- X. Qi, MD, Attending Physician,
- X. Jiang, MD, Attending Physician, Department of Joint Surgery, the Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, Shandong, China.

Correspondence should be sent to Dr X. F. Jiang;
email: lijingcheng63@126.com

doi: 10.1302/2046-3758.67.BJR-2016-0292.R1

Bone Joint Res 2017;6:452–463.
Received: 7 November 2016;
Accepted: 3 March 2017

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.[1] 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.[2] 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).[3] 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)).[4] However, the long-term use of oestrogen replacement therapy significantly increases the risk of breast and ovarian cancer,[5] 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.[6] 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.[7] 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.[8,9] Etidronate (ETI), a first-generation bisphosphonate which inhibits resorption, has the potential to inhibit mineralisation and cause osteomalacia.[10] Studies on the long-term use of ALE have shown that it retains the benefit of successfully reducing bone loss and VF.[11] Additionally, strontium ranelate (STR) is another anti-osteoporotic agent which can stimulate bone formation and reduce resorption.[12] DEN is a potent agent which can reduce the risk of NVF by increasing bone density.[13] Raloxifene (RAL) increases bone mineral density in the spine and femoral neck and reduces risk of vertebral fracture.[14] The beneficial effects of parathyroid hormone (PTH) treatment have also been clearly demonstrated through randomised clinical trials (RCT)[15] 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.[16]

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.[17-19] 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.[20] 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

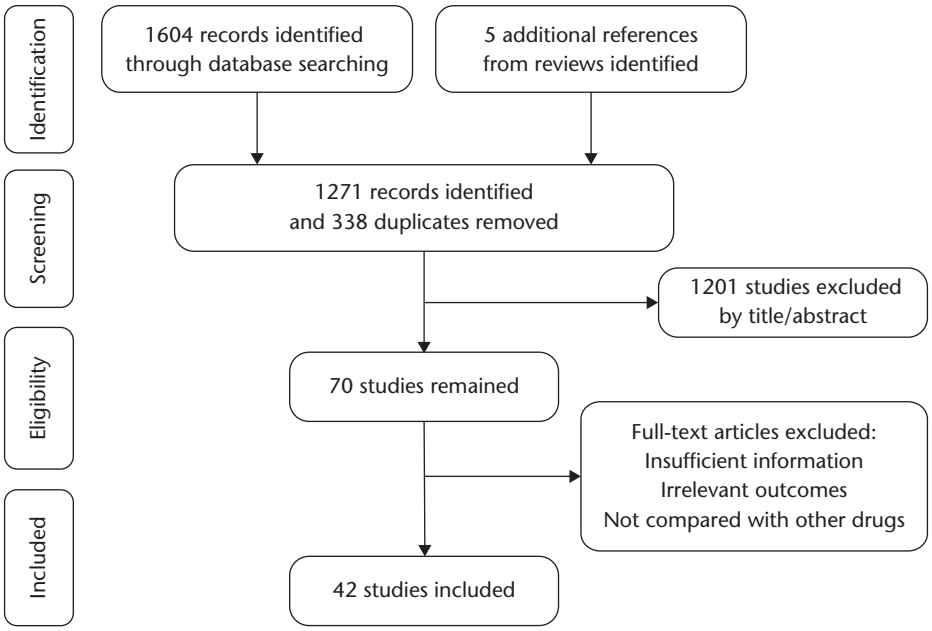

Fig. 1

Flow diagram summarising the results of study identification and selection.

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 Cochran'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 Spieglhalter 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 $\geqslant 20\%$, with an absolute decrease of $\geqslant 4$ 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

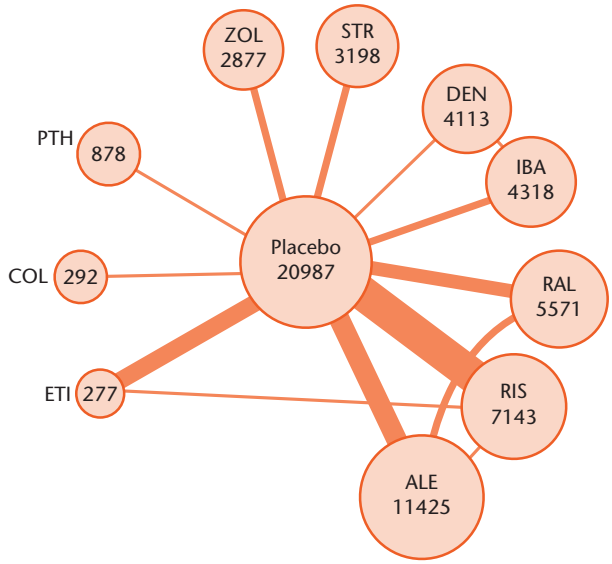

Fig. 2a

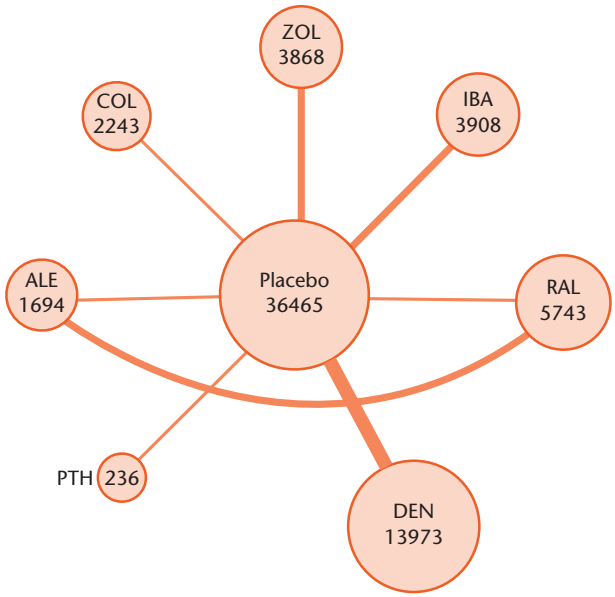

Fig. 2b

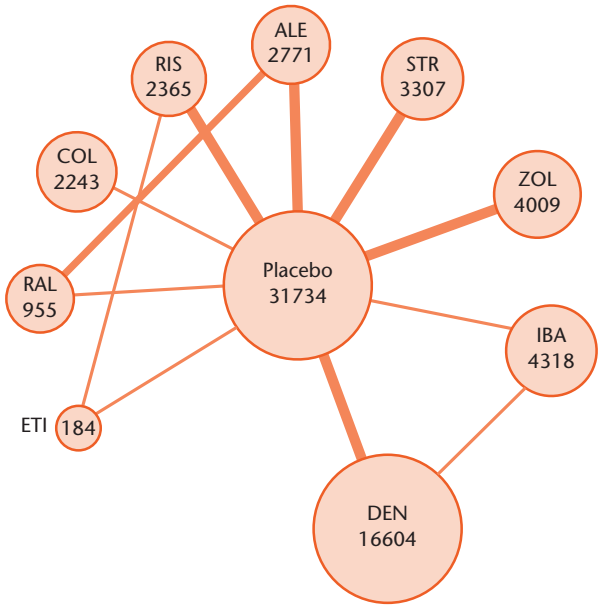

Fig. 2c

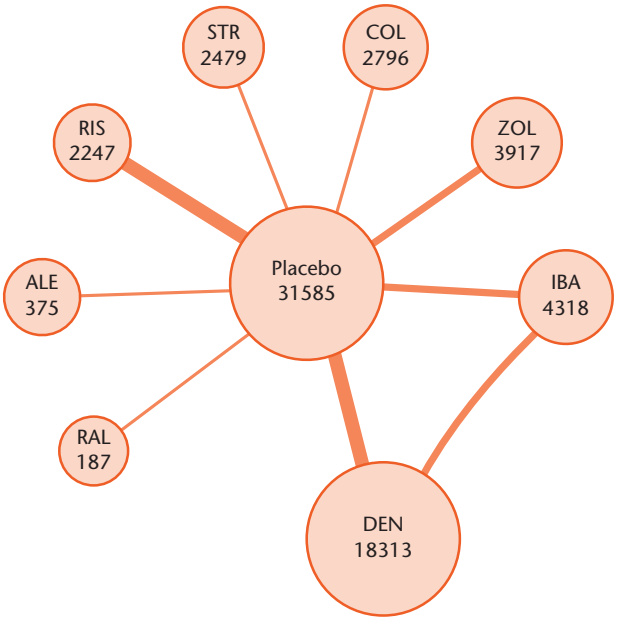

Fig. 2d

Network structures according to (a) new vertebral fractures, (b) clinical vertebral fractures, (c) adverse events, and (d) serious adverse events (ETI, eronate; COL, clodronate; PTH, parathyroid hormone; ZOL, zoledronic acid; STR, strontium ranelate; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; RIS, risedronate; ALE, alendronate; PLA, placebo

exclusion, 42 studies met the criteria and were finally included in our study.[4,13,14,19,26-63] 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

Table I. Characteristics of studies included in the network meta-analysis)

Comparison study information	Study duration (yrs)	Blinding	Mean age (yrs)	Time after menopause (yrs)	Treatment	Regimen dosing*	Patients (n)	Outcome†
ALE *vs* PLA								
Liberman et al[62]	10	√	64/64	16/17	ALE/PLA	5, 10, or 20 mg QD	994	1,4
Bone et al[59]	2	√	71.1/71.1	24.2/22.8	ALE/PLA	1, 2.5, or 5 mg QD	359	1,3,4
Black et al[61]	3	√	71/70.7	NS	ALE/PLA	5 to 10 mg QD	2027	1,2,4
Cummings et al[55]	4.2	√	67.7/67.6	NS	ALE/PLA	5 to 10 mg QD	4432	1
Saag et al[52]	0.92	√	NS	NS	ALE/PLA	5 mg QD	150	1
Adachi et al[47]	2	√	NS	NS	ALE/PLA	5 mg QD	54	1
COL *vs* PLA								
McCloskey et al[42]	3	√	67.5/67.7	NS	COL/PLA	800 mg QD	593	1
McCloskey et al[35]	3	√	79.5/79.6	NS	COL/PLA	800 mg QD	5592	1,3,4
DEN *vs* PLA								
Cummings et al[13]	3	√	72.3/72.3	NS	DEN/PLA		7808	1,2,3,4
Gnant et al[26]	3	√	NS	NS	DEN/PLA	60 mg Q6M	3420	1,3,4
Bone et al[31]	3	√	71.9/71.8	23.7/23.7	DEN/PLA	60 mg Q6M/60 mg Q6M	9100	2,3,4
ETI *vs* PLA								
Lyritis et al[57]	16	Open label	71.8/72.2	25.1/26.4	ETI/PLA	400 mg QD	100	1
Montessori et al[56]		Open label	62.1/62.9	3.4/3.5	ETI/PLA	400 mg QD	71	1
Adachi et al[60]	1	√	NS	NS	ETI/PLA	400 mg QD	70	1,4
Storm et al[63]		√	67.8/68.9	21.2/21.9	ETI (Cyclic)/PLA	400 mg QD	66	1
Shiota et al [45]		NS	60.7/62.7	13.8/15.3	ETI (Cyclic)/PLA	200 mg QD	40	1
IBA *vs* PLA								
Chesnut et al[43]	3	√	69/69	20.9/20.8	IBA/PLA	2.5 mg QD, or 20 mg QOD	2946	1,2,3,4
Chesnut et al[40]	3	√	68.7/68.8	20.8/20.8	IBA/PLA	2.5 mg QD, or 20 um Q2D	2929	1,2,3,4
PTH *vs* PLA								
Neer et al[46]	1.75	√	70/69	NS	PTH/PLA	20, 40 mcg QD	1637	1
Greenspan 2007[36]	1.5	√	NS	NS	PTH/PLA	100 ug QD	471	2
RAL *vs* PLA								
Lufkin et al[54]	1	√	69.9/68.2	22/22.2	RAL/PLA	60, or 120 mg QD	143	1
Ettinger et al[14]	4	√	65/65	17-21/18-21	RAL/PLA	60, or 120 mg QD	6828	1
Morii et al[44]	1	√	65.2/64.7	15.2/15.8	RAL/PLA	60 mg QD/ 120 mg QD	202	1,3,4
Ensrud et al[34]	5.6	√	67.5/67.5	NS	RAL/PLA	60 mg QD	10101	1
RIS *vs* PLA								
Fogelman et al[50]	2	√	65/64	18/17	RIS/PLA	2.5, or 5 mg QD	543	1,3,4
Hooper et al[39]		√	53/52.6	46.1w/46.6w	RIS/PLA	2.5, or 5 mg QD	383	1,3,4
Palomba et al[38]	1	Assess-or blind	52.3/51.4	16.4w/17.5w	RIS/PLA	35 mg QW	81	1
Reginster et al[49]		√	71/71	24/25	RIS/PLA	2.5, or 5 mg QD	1226	1,3,4
Harris et al[51]		√	69/68	24/24	RIS/PLA	5 mg QD	1641	1,3,4
Wallach et al[48]	1	√	64.3/64.2	NS	RIS/PLA	5, or 10 mg QD	255	1
Mortensen et al[53]		√	52.1/51.3	3	RIS/PLA	5 mg QD	111	1
Clemmesen et al[58]		√	68/70	18	RIS/PLA	2.5 mg QD	132	1
STR *vs* PLA								
Meunier et al[41]	3	√	69.2/69.4	21.6/22.1	PLA/STR	2 g QD	1649	1,4
Reginster et al[32]	5	√	76.8/76.7	28.4/28.5	PLA/STR	2 g QD	5091	1,3,4
ZOL *vs* PLA								
Black et al[37]	3	√	73.1/73	NS	ZOL/PLA	5 mg QY	7765	1,2,3,4
Black et al[27]	3	√	78/78.1	NS	ZOL/PLA	5 mg QY	190	1,4
Popp et al[28]	3	√	76.5/77	NS	ZOL/PLA	5 mg QY	110	1,3,4
RAL *vs* ALE								
Recker et al[4]		√	65.5/65.7	18.5/19	RAL/ALE	60 mg QD/10 mg QD	1423	1,2,4
Iwamoto et al[33]	1	√	70.3/68.5	NS	RAL/ALE	60 mg QD/5 mg QD	122	1,4
RIS *vs* ALE								
Thomas et al[29]	1.25	NS	75/76	NS	RIS/ALE		11007	1
RIS *vs* ETI								
Fukunaga[19]		√	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 al[30]	1	NS	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

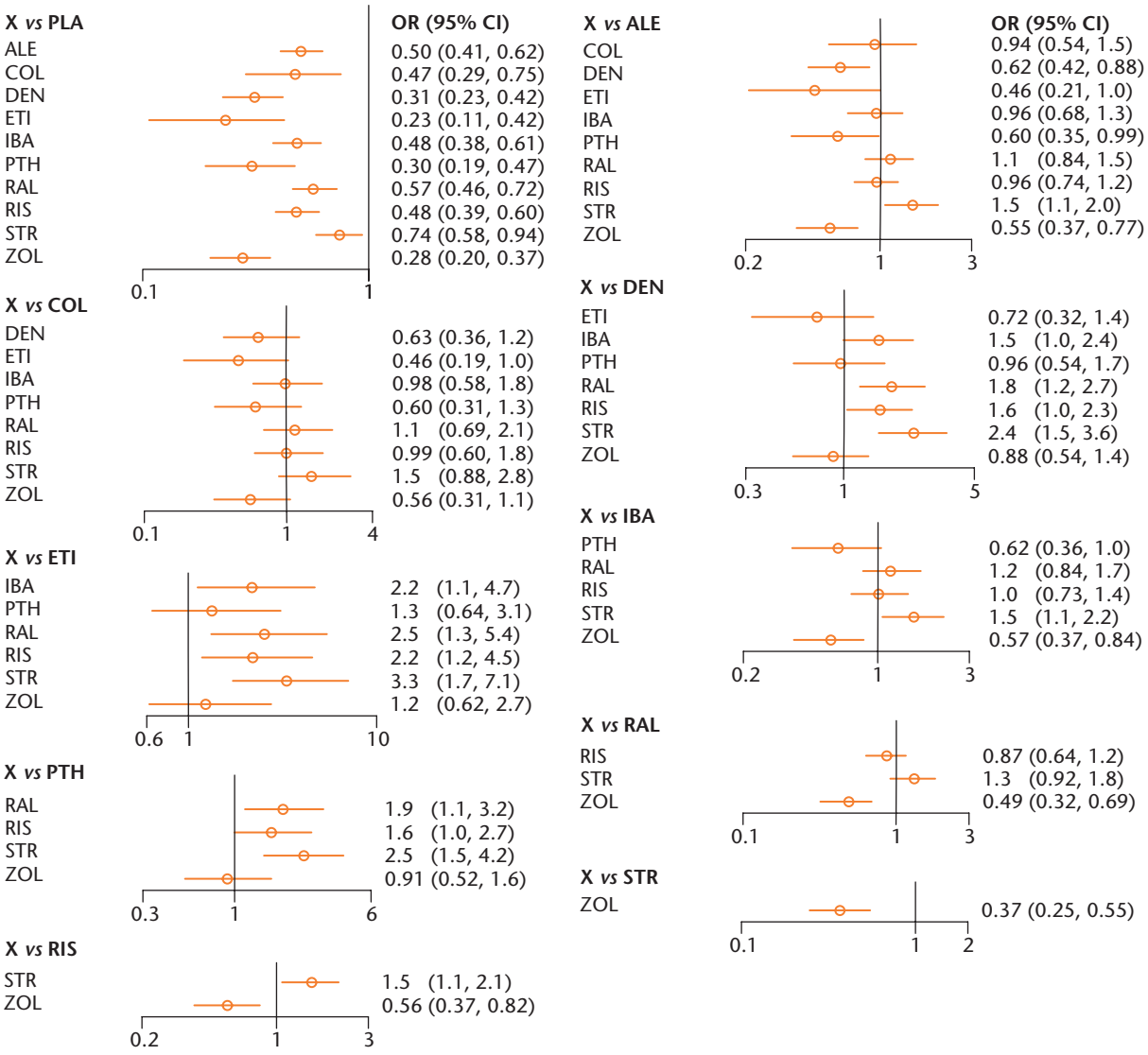

Fig. 3

Forest plot of new vertebral fractures (ETI, eronate; COL, clodronate; PTH, parathyroid hormone; ZOL, zoledronic acid; STR, strontium ranelate; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; RIS, risedronate; ALE, alendronate; PLA, placebo).

a better performance than ALE, IBA, RAL, RIS and STR. Accordingly, ETI, ZOL and PTH came top in overall NVF efficacy. On the other hand, RAL and STR were relatively unsatisfactory because their SUCRA were inferior to many drugs.

CVF. In terms of outcome CVF (Fig. 4 and supplementary Table ii), none of the ten therapies showed a statistically significant superiority to placebo since all 95% CIs include the value one (no effect). Similarly, comparison between different therapies did not exhibit any statistically significant difference.

AEs and SAEs. According to Figure 5, Figure 6 and supplementary Table ii, the results of AEs and SAEs were similar to CVF, in that the performance of all ten therapies in triggering AEs and SAEs did not differ significantly from that of PLA and between different therapies.

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,

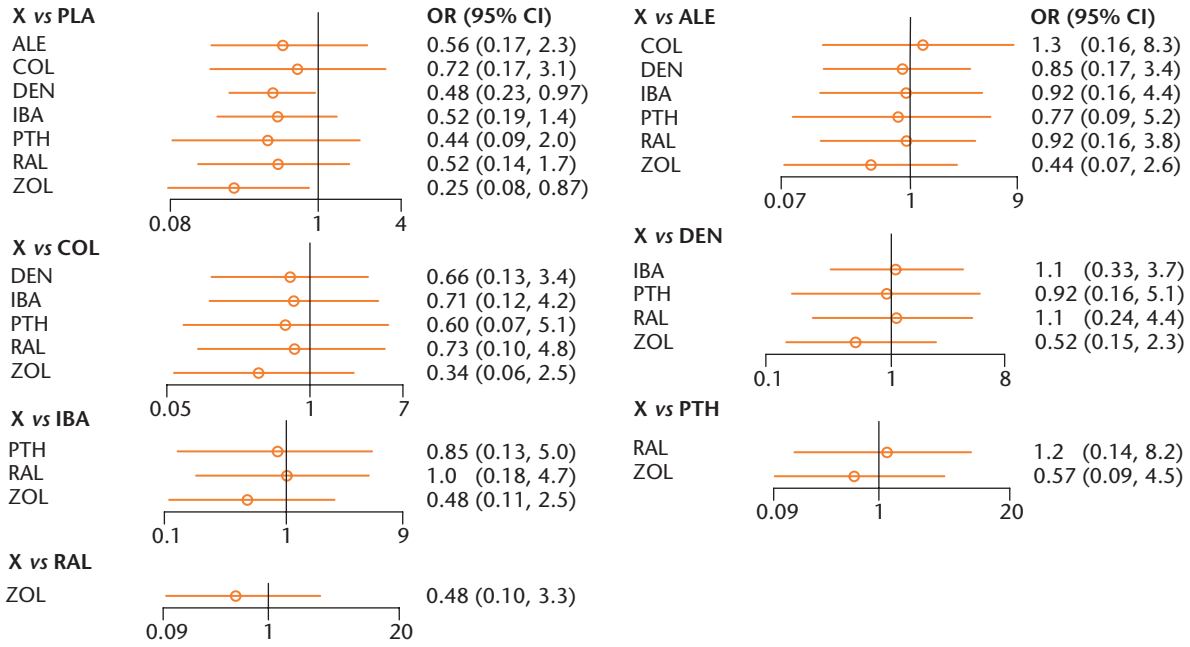

Fig. 4

Forest plot of clinical vertebral fractures (COL, clodronate; PTH, parathyroid hormone; ZOL, zoledronic acid; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; ALE, alendronate; PLA: placebo).

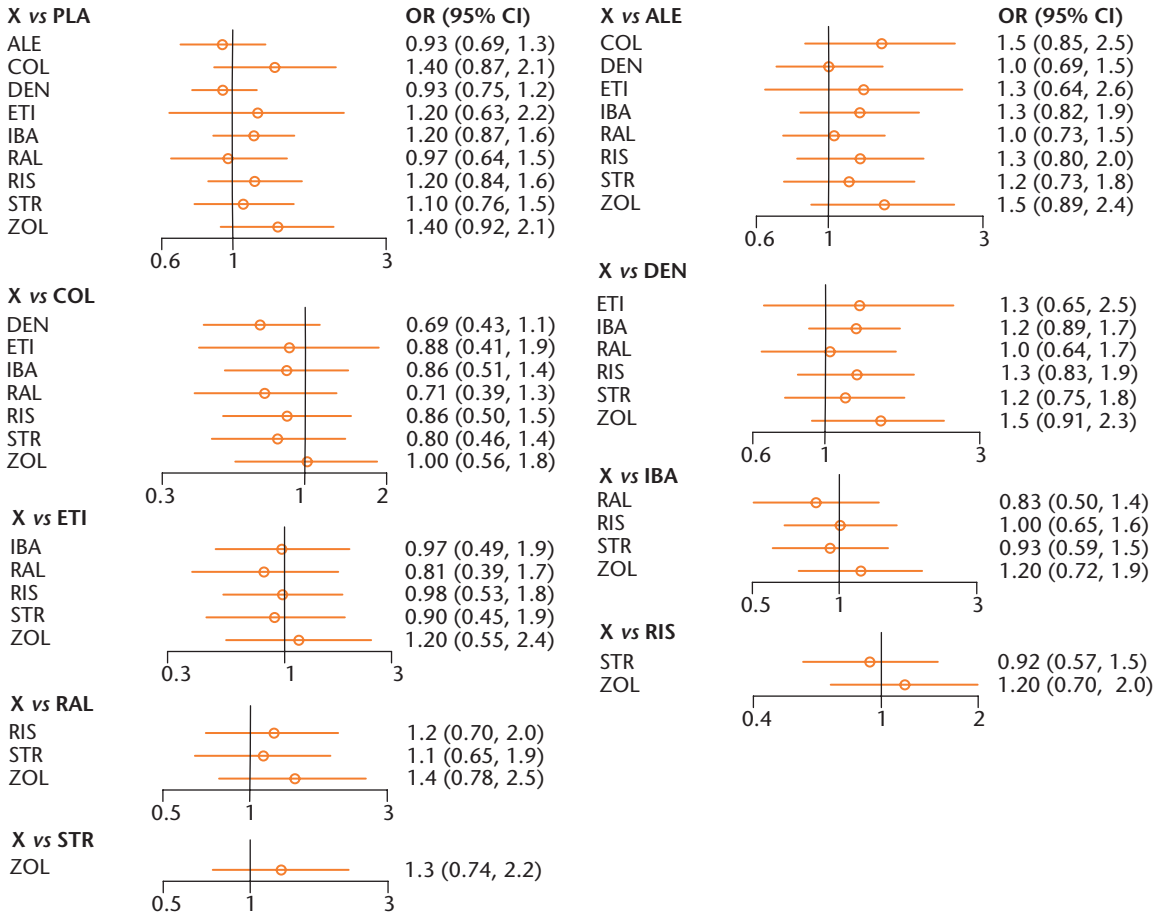

Fig. 5

Forest plot of adverse events (ETI, eronate; COL, clodronate; ZOL, zoledronic acid; STR, strontium ranelate; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; RIS, risedronate; ALE, alendronate; PLA, placebo).

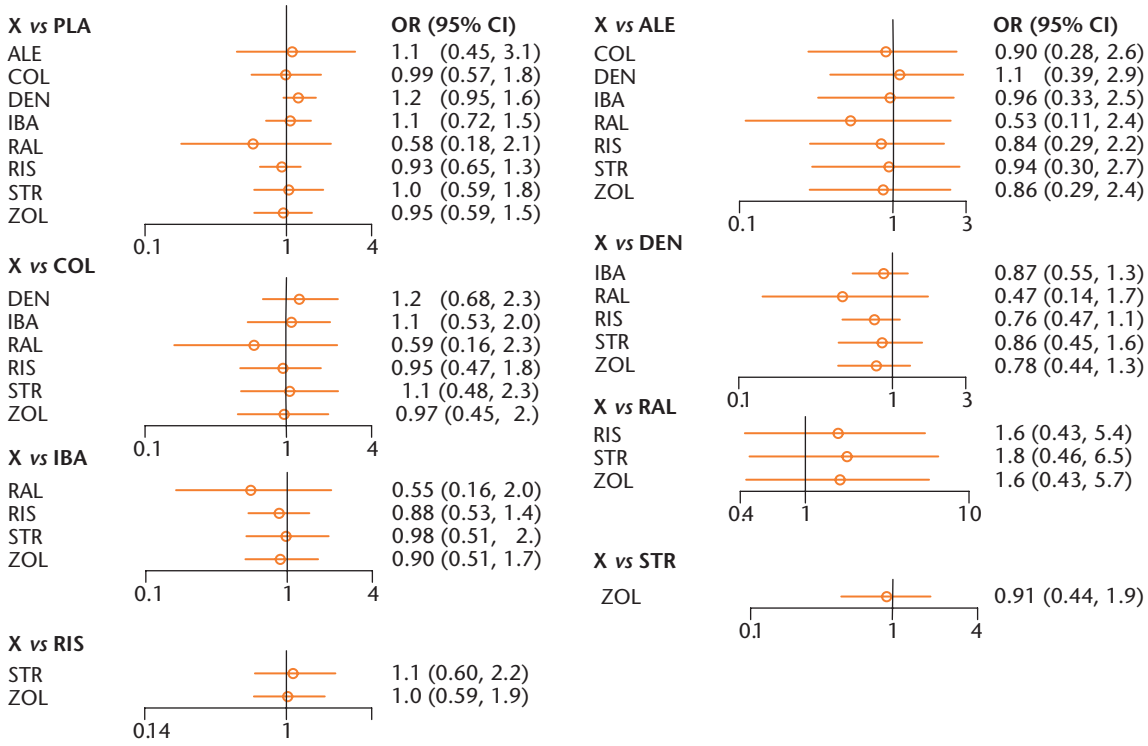

Fig. 6

Forest plot of serious adverse events. 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). NVF 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 NVF. 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 NVF 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 NVF, 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,[64] which drew conclusions from seven RCTs and suggested that ZOL had a 98% probability of reducing the risk of NVF and was more effective than ALE, IBA and RIS. A meta-analysis performed by Cranney et al[65] 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 NVF and presented no statistical difference in AEs and SAEs. This was in accordance with previous studies.[27,30] However, a meta-analysis consisting of approximately nine RCTs and 10 329 participants performed by Anastasilakis et al[66] 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

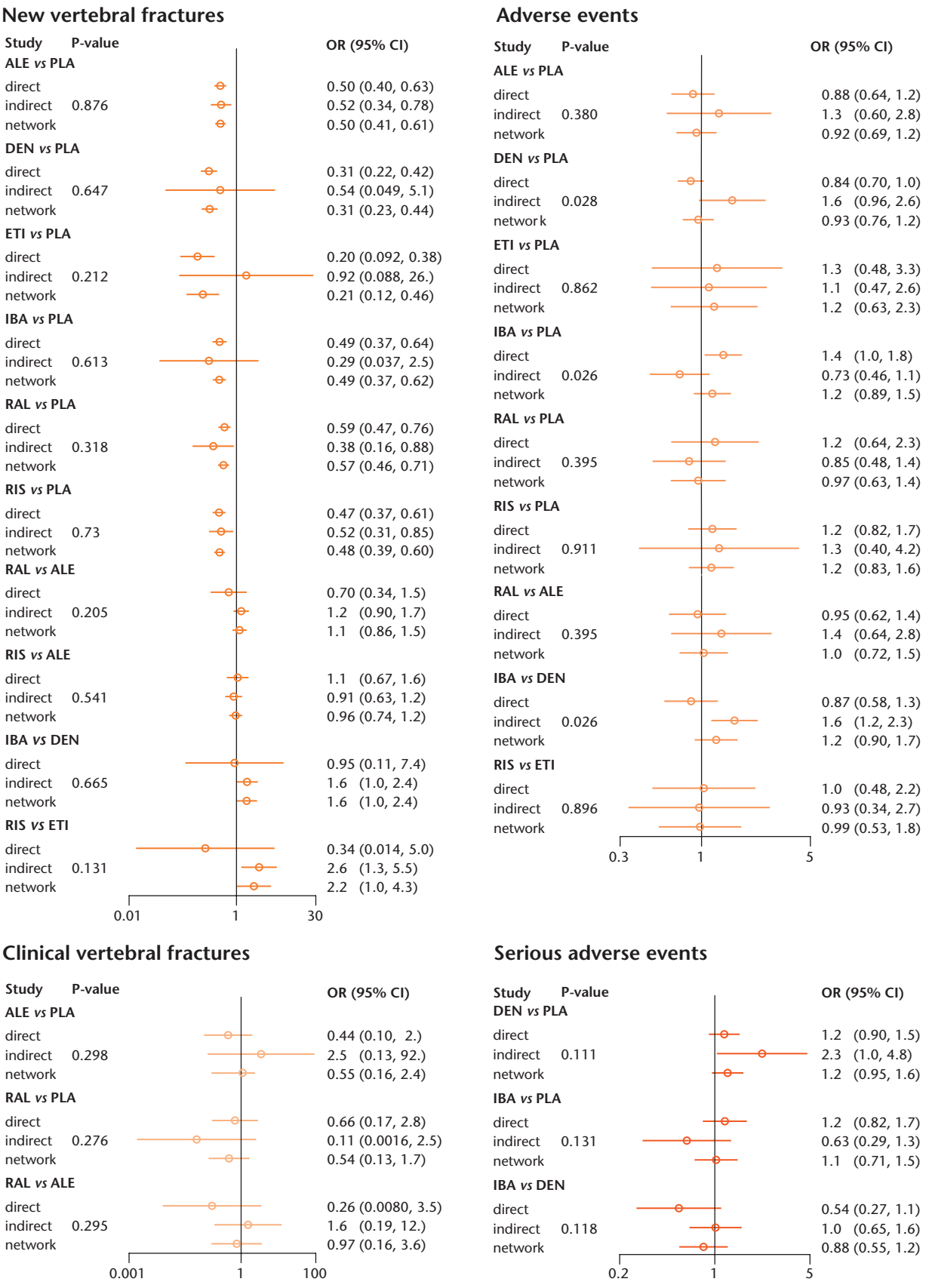

Fig. 7

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).

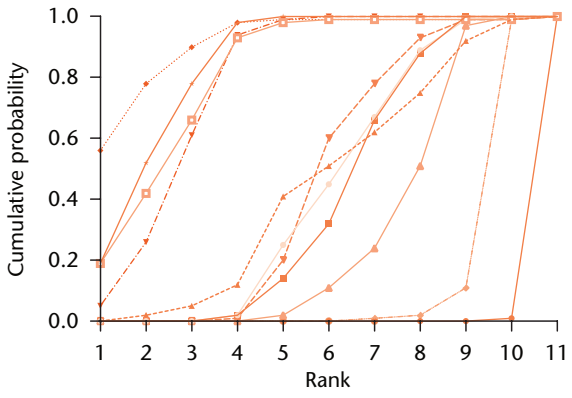

Fig. 8a

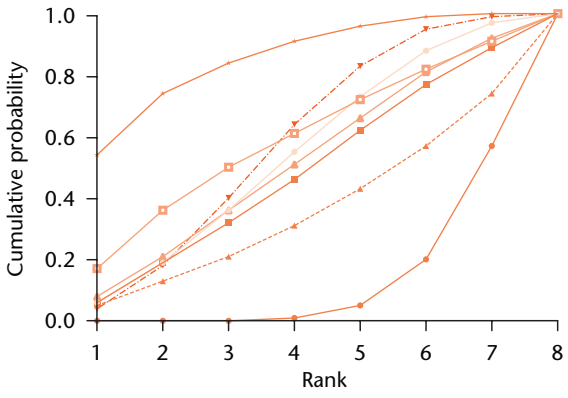

Fig. 8b

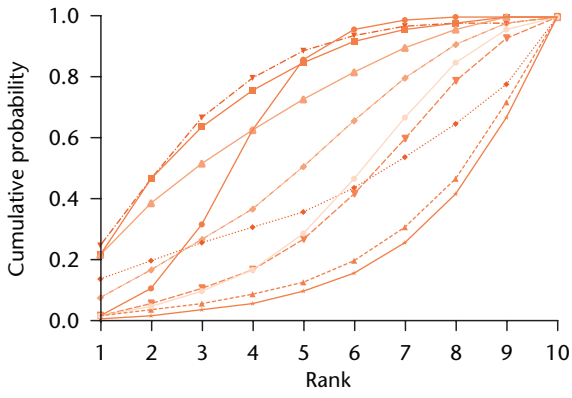

Fig. 8c

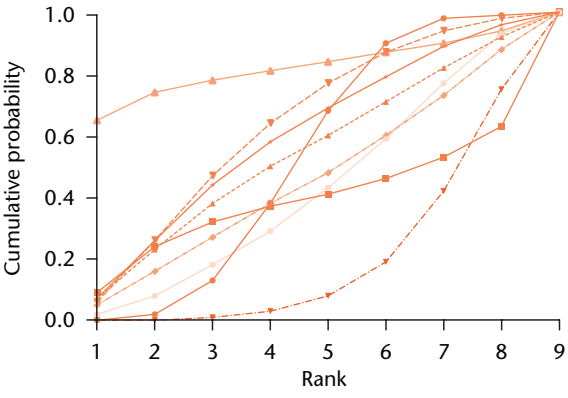

Fig. 8d

SUCRA of new vertebral fractures (a) clinical vertebral fractures (b) adverse events (c) and serious adverse events (d) (ETI, eronate; COL, clodronate; PTH, parathyroid hormone; ZOL, zoledronic acid; STR, strontium ranelate; DEN, denosumab; IBA, ibandronate; RAL, raloxifene; RIS, risedronate; ALE, alendronate; PLA, placebo).

Table II. SUCRA values of all studied interventions with regard to NVF, CVF, AEs, and SAEs

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

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

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.bjr.boneandjoint.org.uk

References

1. **Cummings SR, Melton LJ.** Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359:1761-1767.
2. **Felsenberg D, Silman AJ, Lunt M, et al.** Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). *J Bone Miner Res* 2002;17:716-724.
3. **Mauck KF, Clarke BL.** Diagnosis, screening, prevention, and treatment of osteoporosis. *Mayo Clin Proc* 2006;81:662-672.
4. **Recker RR, Kendler D, Recknor CP, et al.** Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone* 2007;40:843-851.
5. **Manson JE, Hsia J, Johnson KC, et al.** Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534.
6. **Watson J, Wise L, Green J.** Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005. *Eur J Clin Pharmacol* 2007;63:843-849.
7. **Paggiosi MA, Peel N, McCloskey E, Walsh JS, Eastell R.** Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int* 2014;25:2729-2741.
8. **Ghinoi V, Brandi ML.** Clodronate: mechanisms of action on bone remodelling and clinical use in osteometabolic disorders. *Expert Opin Pharmacother* 2002;3:1643-1656.
9. **Frediani B, Cavalieri L, Cremonesi G.** Clodronic acid formulations available in Europe and their use in osteoporosis: a review. *Clin Drug Investig* 2009;29:359-379.
10. **Fleisch HA.** Bisphosphonates: preclinical aspects and use in osteoporosis. *Ann Med* 1997;29:55-62.
11. **Black DM, Schwartz AV, Ensrud KE, et al; FLEX Research Group.** Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006;296:2927-2938.
12. **Buehler J, Chappuis P, Saffar JL, Tsouderos Y, Vignery A.** Strontium ranelate inhibits bone resorption while maintaining bone formation in alveolar bone in monkeys (Macaca fascicularis). *Bone* 2001;29:176-179.
13. **Cummings SR, San Martin J, McClung MR, et al.** Denosumab for prevention of fractures in post-menopausal women with osteoporosis. *N Engl J Med* 2009;361:756-765.
14. **Ettinger B, Black DM, Mitlak BH, et al.** Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;282:637-645.
15. **Verhaar HJ, Lems WF.** PTH analogues and osteoporotic fractures. *Expert Opin Biol Ther* 2010;10:1387-1394.
16. **Henriksen K, Andersen JR, Riis BJ, et al.** Evaluation of the efficacy, safety and pharmacokinetic profile of oral recombinant human parathyroid hormone [rhPTH(1-31)NH(2)] in postmenopausal women with osteoporosis. *Bone* 2013;53:160-166.
17. **Wang C.** Efficacy and Safety of Zoledronic Acid for Treatment of Post-menopausal Osteoporosis: A Meta-Analysis of Randomized Controlled Trials. *Am J Ther* 2016 (Epub ahead of print) PMID: 26938765.
18. **Serrano AJ, Begoña L, Anitua E, Cobos R, Orive G.** Systematic review and meta-analysis of the efficacy and safety of alendronate and zoledronate for the treatment of postmenopausal osteoporosis. *Gynecol Endocrinol* 2013;29:1005-1014.
19. **Fukunaga M, Kushida K, Kishimoto H, et al.** A comparison of the effect of risedronate and etidronate on lumbar bone mineral density in Japanese patients with osteoporosis: a randomized controlled trial. *Osteoporos Int* 2002;13:971-979.
20. **Bucher HC, Guyatt GH, Griffith LE, Walter SD.** The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683-691.
21. **Mantel N, Haenszel W.** Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-748.
22. **DerSimonian R, Laird N.** Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;45:139-145.
23. **van de Schoot R, Kaplan D, Denissen J, et al.** A gentle introduction to bayesian analysis: applications to developmental research. *Child Dev* 2014;85:842-860.
24. **Spiegelhalter DJ, Freedman LS, Parmar MK.** Applying Bayesian ideas in drug development and clinical trials. *Stat Med* 1993;12:1501-1511.
25. **Jansen JP, Fleurence R, Devine B, et al.** Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011;14:417-428.
26. **Gnant M, Pfeiler G, Dubsky PC, et al.** Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;386:433-443.
27. **Black DM, Reid IR, Cauley JA, et al.** The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2015;30:934-944.
28. **Popp AW, Buffat H, Cavelti A, et al.** Cortical bone loss at the tibia in postmenopausal women with osteoporosis is associated with incident non-vertebral fractures: results of a randomized controlled ancillary study of HORIZON. *Maturitas* 2014;77:287-293.
29. **Thomas T, Horlait S, Ringe JD, et al.** Oral bisphosphonates reduce the risk of clinical fractures in glucocorticoid-induced osteoporosis in clinical practice. *Osteoporos Int* 2013;24:263-269.
30. **Recknor C, Czerwinski E, Bone HG, et al.** Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol* 2013;121:1291-1299.
31. **Bone HG, Chapurlat R, Brandi ML, et al.** The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. *J Clin Endocrinol Metab* 2013;98:4483-4492.
32. **Reginster JY, Felsenberg D, Boonen S, et al.** Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. *Arthritis Rheum* 2008;58:1687-1695.
33. **Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H.** Comparison of effects of alendronate and raloxifene on lumbar bone mineral density, bone turnover, and lipid metabolism in elderly women with osteoporosis. *Yonsei Med J* 2008;49:119-128.
34. **Ensrud KE, Stock JL, Barrett-Connor E, et al.** Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. *J Bone Miner Res* 2008;23:112-120.
35. **McCloskey EV, Beneton M, Charlesworth D, et al.** Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. *J Bone Miner Res* 2007;22:135-141.
36. **Greenspan SL, Bone HG, Ettinger MP, et al.** Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med* 2007;146: 326-339.
37. **Black DM, Delmas PD, Eastell R, et al.** Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-1822.
38. **Palomba S, Orio F, Jr, Manguso F, et al.** Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. *Osteoporos Int* 2005;16:1141-1149.
39. **Hooper MJ, Ebeling PR, Roberts AP, et al.** Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. *Climacteric* 2005;8:251-262.

40. **Chesnut CH, Ettinger MP, Miller PD, et al.** Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. *Curr Med Res Opin* 2005;21:391-401.
41. **Meunier PJ, Roux C, Seeman E, et al.** The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459-468.
42. **McCloskey E, Selby P, Davies M, et al.** Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004;19:728-736.
43. **Chesnut CH, III, Skag A, Christiansen C, et al.** Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19:1241-1249.
44. **Morii H, Ohashi Y, Taketani Y, et al.** Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. *Osteoporos Int* 2003;14:793-800.
45. **Shiota E, Tsuchiya K, Yamaoka K, Kawano O.** Effect of intermittent cyclical treatment with etidronate disodium (HEBP) and calcium plus alphacalcidol in postmenopausal osteoporosis. *J Orthop Sc.* 2001;6:133-136.
46. **Neer RM, Arnaud CD, Zanchetta JR, et al.** Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-1441.
47. **Adachi JD, Saag KG, Delmas PD, et al.** Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001;44:202-211.
48. **Wallach S, Cohen S, Reid DM, et al.** Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 2000;67:277-285.
49. **Reginster J, Minne HW, Sorensen OH, et al.** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000;11:83-91.
50. **Fogelman I, Ribot C, Smith R, et al.** Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000;85:1895-1900.
51. **Harris ST, Watts NB, Genant HK, et al.** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;282:1344-1352.
52. **Saag KG, Emkey R, Schnitzer TJ, et al.** Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med* 1998;339:292-299.
53. **Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC, Jr.** Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab* 1998;83:396-402.
54. **Lufkin EG, Whitaker MD, Nickelsen T, et al.** Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998;13:1747-1754.
55. **Cummings SR, Black DM, Thompson DE, et al.** Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-2082.
56. **Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker K.** The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. *Osteoporos Int* 1997;7:52-58.
57. **Lyritis GP, Tsakalakos N, Paspati I, et al.** The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. *Clin Rheumatol* 1997;16:354-360.
58. **Clemmesen B, Ravn P, Zegels B, et al.** A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. *Osteoporos Int* 1997;7:488-495.
59. **Bone HG, Downs RW, Jr, Tucci JR, et al.** Dose-response relationships for alendronate treatment in osteoporotic elderly women. *J Clin Endocrinol Metab* 1997;82:265-274.
60. **Adachi JD, Bensen WG, Brown J, et al.** Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337:382-387.
61. **Black DM, Cummings SR, Karpf DB, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535-1541.
62. **Liberman UA, Weiss SR, Bröll J, et al.** Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333:1437-1443.
63. **Storm T, Thamsborg G, Steiniche T, Genant HK, Sørensen OH.** Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265-1271.
64. **Jansen JP, Bergman GJ, Huels J, Olson M.** Prevention of vertebral fractures in osteoporosis: mixed treatment comparison of bisphosphonate therapies. *Curr Med Res Opin* 2009;25:1861-1868.
65. **Cranney A, Guyatt G, Krolicki N, et al.** A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2001;12:140-151.
66. **Anastasilakis AD, Toulis KA, Goulis DG, et al.** Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. *Horm Metab Res* 2009;41:721-729.
67. **Emkey R, Koltun W, Beusterien K, et al.** Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin* 2005;21:1895-1903.
68. **Ringe JD.** Development of clinical utility of zoledronic acid and patient considerations in the treatment of osteoporosis. *Patient Prefer Adherence* 2010;4:231-245.

Funding Statement
- None declared.

*G. Wang and L. Sui contributed equally to this study and are first co-authors.

Author Contributions
- G. Wang: Interviews, Data collection and analysis
- L. Sui: Study inception, Preparing the paper.
- P. Gai: Study inception, Preparing the paper.
- G. Li: Data analysis, Preparing the paper.
- X. Qi: Study inception, Preparing the paper, Guarantor of study.
- X. Jiang: Study inception, Preparing the paper, Guarantor.

Conflicts of Interest Statement
- None declared.