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Drug efficacies on bone mineral density and fracture rate for the treatment of postmenopausal osteoporosis: a network meta-analysis

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Abstract. – OBJECTIVE: Globally, a great number of elderly suffer from osteoporosis, especially postmenopausal women. Osteoporosis results in low bone mineral density (BMD) and high risk of fragility fracture. However, there is no defined strategy to select the most suitable anti-osteoporotic drugs for osteoporosis patients. Therefore, this study aims to select the most effective anti-osteoporotic drug for postmenopausal women with osteoporosis.

MATERIALS AND METHODS: Literature search was conducted in PubMed, EMBASE, and the Cochrane Library. Raw data from the related randomized clinical trials were extracted. A pairwise and network meta-analysis model was utilized to assess the efficacy of ten drugs on the percentage change of BMD in the lumbar spine and total hip from baseline to one year of treatment. Risks of vertebral fracture and non-vertebral fracture were evaluated as well. We reported the effect size with a weighted mean difference (WMD) for continuous outcomes and odds ratio (OR) for dichotomous outcomes. All the drugs were ranked based on the surface under the cumulative ranking curve (SUCRA) value. Furthermore, the heterogeneity, consistency and publication bias of enrolled literature were assessed.

RESULTS: With regard to lumbar spine BMD, the ten selected drugs all showed significant efficacy compared with placebo. In regard to total hip BMD and vertebral fracture, with the exception of calcitonin, the remaining nine drugs all showed significant efficacy compared with placebo. Six drugs – abaloparatide, alendronate, risedronate, strontium ranelate, teriparatide, and zoledronate – were significantly more effective compared with placebo for the treatment of non-vertebral fractures. As the SUCRA values indicated, abaloparatide performed the best on improving lumbar spine BMD, vertebral fracture and non-vertebral fracture, while denosumab was the best choice to improve total hip BMD.

CONCLUSIONS: To sum up, abaloparatide, denosumab, and teriparatide showed the best efficacy for the treatment of postmenopausal osteoporosis, especially abaloparatide.

Key Words
Postmenopausal osteoporosis, Abaloparatide, Denosumab, Teriparatide, Network meta-analysis.

Introduction

Osteoporosis is a systemic skeletal disease in which increased bone weakness highlights the risk of fracture[1]. It is associated with a significant social and public health burden. Elderly women are more likely to suffer from this disease since the reduced estrogen levels after menopause contributes to a rapid decline in bone mass[2,3]. According to the National Osteoporosis Foundation, there are approximately 9.1 million osteoporosis women and an additional 26 million women with low bone mass in America, which is far more than the estimated 2.8 million osteoporosis men and 14.4 million men with low bone mass. Several prospective studies[4,5] suggested that improved bone mineral density (BMD) is associated with a reduction in the fracture rate. Hence, improving BMD and reducing fracture are the primary therapeutic goals.

There are two main categories of therapies applied to prevent or treat postmenopausal osteoporosis. One is anti-resorptive agents containing estrogen or selective estrogen receptor modulators (bazedoxifen, raloxifene), calcitonin, bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), denosumab, and odanacatib. The other category is the drugs which have anabolic effects on bone such as strontium ranelate, PTH1-84, and PTH1-34 (teriparatide)[6]. Recently, a new drug abaloparatide, which is also a parathyroid hormone-related protein analog drug similar to teriparatide, has completed the Phase III trial and exerts a marked effect on the improvement of BMD and fracture rate[7].

There are multiple therapies for postmenopausal osteoporosis. Previously, randomized clinical

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trials (RCTs) and traditional pairwise meta-analyses have been performed to determine the most effective one. However, the conclusions remain controversial. Therefore, a network meta-analysis (NMA) is necessary for identifying the most effective therapy[8]. However, one previously-published NMA[9] had some drawbacks because it included some sub-standard trials reporting osteoporosis induced by glucocorticoid treatment or male osteoporosis. Furthermore, some other articles[10,11] only assessed a few drugs and the sample size was small.

Therefore, we conducted this NMA in order to evaluate the comparative efficacy of ten primary drugs in postmenopausal women with osteoporosis, including abaloparatide (ALE), alendronate (ALE), calcitonin (CT), denosumab (DEN), ibandronate (IBA), risedronate (RIS), raloxifene (RLX), strontium ranelate (STR), teriparatide (TPD), and zoledronate (ZOL). The efficacy of the ten drugs on percentage change of BMD from baseline to one-year treatment in the lumbar spine and total hip, vertebral fracture (VF) rate and non-vertebral fracture (NVF) rate was assessed.

Materials and Methods

Search Strategy

Literature search and identification process were conducted in PubMed, EMBASE, and the Cochrane Library from inception until April 18, 2018 (date of final search). Articles published in both English and Chinese languages were searched using the following medical subject headings: "Osteoporosis, Postmenopausal, Abaloparatide, Alendronate, Calcitonin, Denosumab, Ibandronate, Risedronate, Raloxifene, Strontium Ranelate, Teriparatide, Zoledronate, randomized controlled trial", and their synonyms. The search procedures were performed by two independent reviewers. Reference lists of acquired articles were manually searched.

Inclusion and Exclusion Criteria

Studies meeting the following criteria were included: (1) A randomized controlled trial; (2) Subjects were postmenopausal women with osteoporosis; (3) The study was designed to compare the effects of the following drugs with placebo (PLA) or between each other: ABL, ALE, CT, DEN, IBA, RIS, RLX, STR, TPD, ZOL; (4) At least one of the following outcomes was assessed in each study: percentage change of BMD from baseline to one-year treatment of the lumbar spine or total hip, VF and NVF; (5) Sufficient data should be provided in the original studies.

Exclusion data were applied: (1) Men or premenopausal women were included in the study; (2) Participants were treated by combined therapy or sequential therapy; (3) The duration of follow-up was less than 12 months.

Data Extraction and Quality Assessment

Data extracted from the included studies were assessed independently by two reviewers (San Zhang, Si Li), with discussion to the third reviewer (Er Wang) to resolve any discrepancies. Information including the name of first author, year of publication, sample size, comparators, drug dosage, mean age of patients, blinding condition, outcomes of the study and maximum follow-up time were extracted. The quality of the included studies was assessed according to the modified JADAD score (out of 7). The studies gaining scores of 4 to 7 were considered as high-quality and regarded as low-quality if they gained a score of 1 to 3[12].

Statistical Analysis

Four outcomes (lumbar spine BMD, total hip BMD, VF, and NVF) were analyzed. Pairwise meta-analysis of studies that directly compared different treatments was conducted using STATA 14.0 (Stata Corp., College Station, TX, USA) software. The percentage change of BMD in the lumbar spine and total hip was reported using the weighted mean difference (WMD) and the 95% confidence interval (95% CI). The risk of vertebral fracture and non-vertebral fracture was reported using the odds ratio (OR) and the 95% confidence interval (95% CI). Cochran's Q test and Higgins' I-squared test were used to test the heterogeneity of enrolled studies. A *p*-value of the Cochran's Q test statistic less than 0.05 or I-square larger than 50% indicated significant heterogeneity among included studies for each pairwise comparison. The fixed-effect model was applied for studies without significant heterogeneity and otherwise, the random-effects model was applied.

Next, the network meta-analysis was performed by Bayesian analysis methods using R software (Version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria)[13]. The effect sizes of WMD and OR and their corresponding 95% confidence intervals (95% CI) were calculated with a random-effects model. In order to evaluate the consistency of the network meta-analysis model, the node-splitting method was utilized to assess the difference between direct and indirect comparisons. Furthermore, the

effects of drugs were ranked by the surface under the cumulative ranking (SUCRA) curve values[14]. Higher SUCRA value indicated the pronounced efficacy of the drug. Funnel plots were depicted to evaluate the risk of publication bias of the studies included in this review.

Results

Study Selection and Study Characteristics

A total of 13,542 articles were initially searched and three articles were identified from other reviews. After removal of 4,874 duplicate references, 8,671 articles remained. Of these, 644 full-text articles were retrieved after 8,027 articles were excluded by reviewing the title and abstract. Another 540 articles were removed for other reasons (e.g., combined therapy or sequential therapy, unrelated drugs or diseases other than osteoporosis, re-analysis or extension of primary studies, duration of follow-up < 12 months, irrelevant outcomes). 106 articles were excluded due to lack of complete data. As a result, a total of 103 studies were included[7,15-116]. Details of the literature selection process were shown in Figure 1. The networks of the comparisons of four outcomes were presented in Figure 2.

The following drugs were analyzed for their efficacy: ABL, ALE, CT, DEN, IBA, RIS, RLX, STR, TPD, and ZOL. A total of 103 studies involving 122,685 participants with postmenopausal osteoporosis. Six of the 103 studies were three-arm studies and the remaining studies were two-arm ones. The treatment, drug dosage, mean age and follow-up time of each study were summarized in Table I.

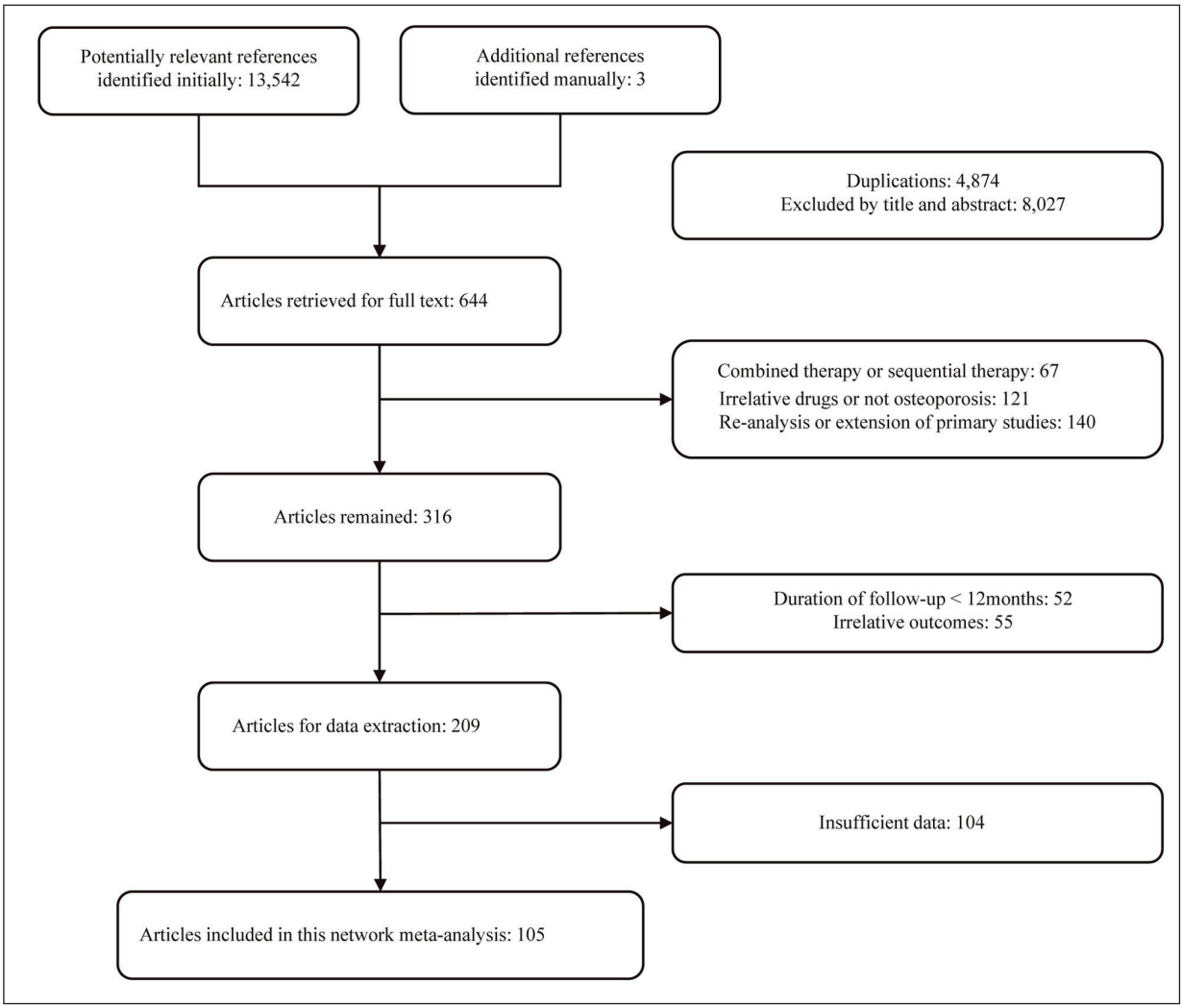

Figure 1. Study flow and selection diagram.

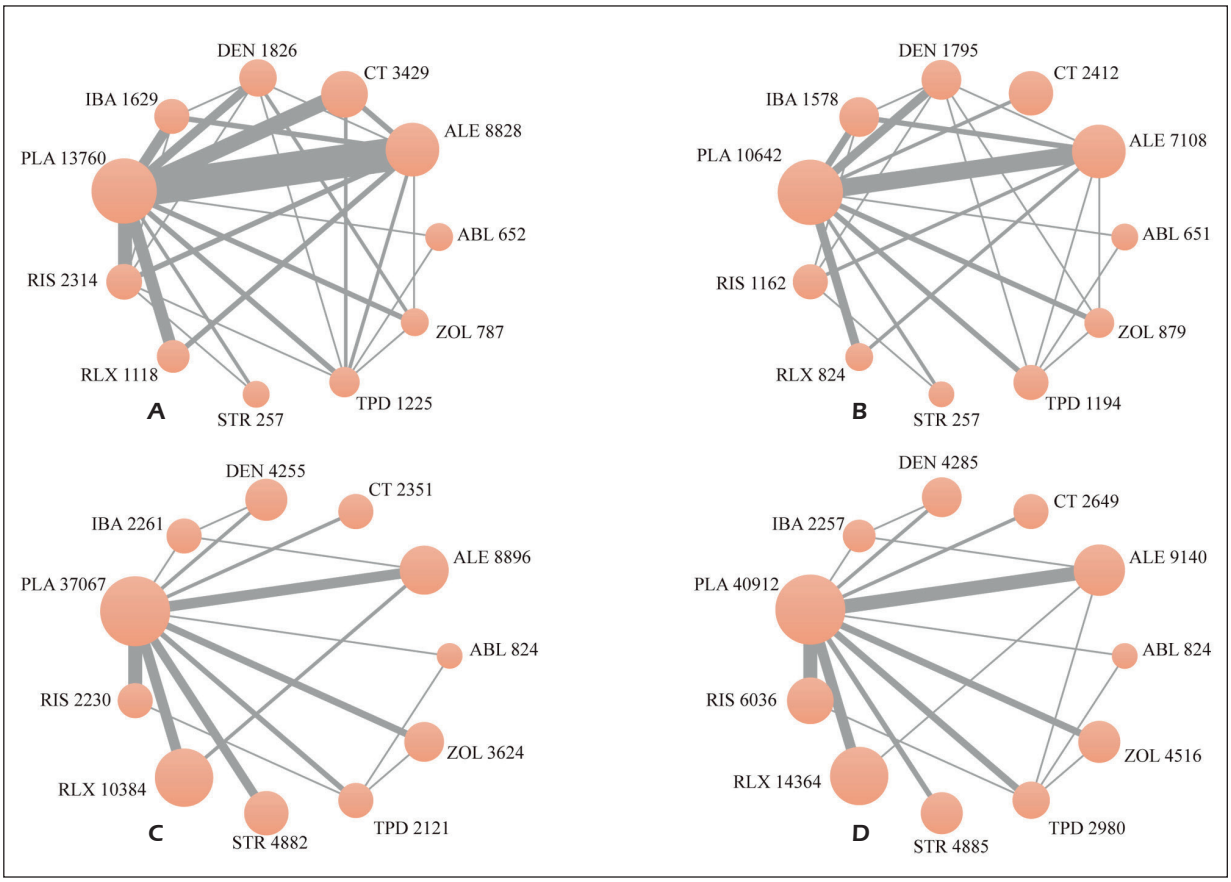

Figure 2. Evidence network of eligible comparisons for network meta-analysis. The width of the lines is proportional to the number of trials comparing each pair of treatments; the area of circles represents the cumulative number of patients for each intervention, **A**, Lumbar spine BMD, **B**, Total hip BMD, **C**, Vertebral fracture, and **D**, Non-vertebral fracture.

Results of Pairwise Meta-Analysis

Lumbar spine BMD

Results of lumbar spine BMD in the pairwise meta-analysis were presented in Table II. Compared with PLA, nine drugs significantly increased the lumbar spine BMD: ABL (WMD = 9.31, 95% CI = 8.62-10.00), ALE (4.58, 4.14-5.02), DEN (5.32, 4.91-5.73), IBA (3.54, 2.78-4.30), RIS (2.85, 2.07-3.63), RLX (2.26, 1.90-2.62), STR (5.13, 3.39-6.87), TPD (6.35, 3.77-8.93) and ZOL (3.56, 2.19-4.93). Among the ten drugs, ALE performed better than CT (3.95, 3.14-4.77) and RLX (2.86, 1.88-3.85), but worse than ZOL (–8.08, -10.60-–5.56). DEN outperformed IBA (2.11, 1.56-2.66), RIS (2.30, 1.76-2.84) and ZOL (2.03, 1.51-2.55). Similarly, TPD was superior to CT (4.11, 3.73-4.49), RIS (2.69, 1.12-4.26) and ZOL (2.75, 1.56-3.94); however, it was inferior to ABL (–1.48, -2.12-–0.84). In addition, IBA was better than RIS (2.51, 1.34-3.68).

Total hip BMD

Results of total hip BMD in the pairwise meta-analysis were presented in Table III. Similar to lumbar spine BMD, nine drugs with significant effects increased total hip BMD compared with PLA: ABL (WMD = 3.35, 95% CI = 3.02-3.68), ALE (2.39, 2.01-2.77), CT (0.53, 0.32-0.74), DEN (3.18, 2.91-3.45), IBA (1.83, 1.21-2.44), RLX (1.43, 0.93-1.92), STR (3.26, 2.62-3.90), TPD (2.31, 2.01-2.61) and ZOL (2.70, 2.28-3.11). Among the ten drugs, ALE was more effective than RIS (1.09, 0.69, 1.49) and RLX (1.21, 0.78-1.64) but less effective than DEN (–1.44, –2.41-–0.47), TPD (-2.41, -3.97-–0.85) and ZOL (-3.70, -4.22-–3.18). Furthermore, DEN achieved a better performance than IBA (1.18, 0.81-1.55), RIS (1.56, 1.22-1.90), TPD (1.84, 0.41-3.27) and ZOL (1.31, 0.90-1.72). Meanwhile, TPD was inferior to ZOL (–1.08, –1.93-–0.23).

Table I. Key features of included studies.

Trial	Mean age (yrs)	Dosage*	Sample size	Follow-up (yrs)	Years after menopausal (yrs)	Out-come#
ABL/TPD/PLA						
Miller 2016	68.9/68.7	20 ug QD/80 ug QD	2463	1.5	20.6/20.4/19.9	1,2,3,4
ALE/CT/PLA						
Dursun 2001	60.2/63.2/60.6	10 mg QD/100 IU QD	150	1	14.32/17.56/14.88	1
Downs 2000	64.6/64.1/64.6	10 mg QD/200 IU QD	299	1	16.5/16.1/16.5	1
Adami 1993	59/60/59	10–20 mg QD/100 IU QD	286	2	NS	1
ALE/DEN/PLA						
Lewiecki 2007	62.8/62.3/63.7	70 mg QW/6–210 mg Q6M	412	2	NS	1,2
ALE/IBA/RIS						
Paggiosi 2014	67.8/66.9/66.8	70 mg QW/150 mg QM/35 mg QW	172	2	19.2/17.4/16.4	1,2
ALE/IBA						
Miller 2008'	65.6/65.6	70 mg QW/150 mg QM	1760	1	18.2/18.5	3,4
Guanabens 2013	65.5/63.6	70 mg QW/150 mg QM	42	2	NS	1,2
ALE/PLA						
Yen 2000	59/60.3	10 mg QD	46	1	11.7/11.8	1
Stpan 1999	59.3/60.9	10 mg QD	30	1	14.4/14.4	1
Chesnut 1995	62.9/63.6	5–40 mg QD	188	2	15.0/16.9	1,2
Yan 2009	65.2/64.6	70 mg QW	560	1	15.36/15.14	1,2,4
Pols 1999	62.8/62.8	10 mg QD	1908	1	15.8/15.9	1,2,4
Devogelaer 1996	61.2/62.7	5–20 mg QD	516	3	16/15.2	1
Liberman 1995	64/64	5–20 mg QD	994	3	16/17	1,3,4
Tucci 1996	63.9/64.2	5–20 mg QD	392	3	17.1/17.8	1
Hochberg 2005	69.1/69.3	5 mg QD	5093	2	23.1/23.1	3,4
Quandt 2005	60.6/70.2	5–10 mg QD	3737	4.5	23.4/24.1	2
Rossini 2001	72/74	10 mg QD	26	2	23/24	1,2
Bone 1997	70.8/71.1	1–5 mg QD	359	2	24.8/22.8	1,3,4
Lau 2000	74/74	10 mg QD	78	1	24/24	1,2
Hosking 1998	53/53	2.5–5 mg QD	1358	2	6/6	1,2,4
Ravn 1999	55/55	2.5–5 mg QD	1609	4	9/8	1,2
Black 1996	71/70.7	5 mg QD	2027	3	NS	1,2,3,4
Cummings 1998	67.6/67.7	5 mg QD	4432	4	NS	1,2,3,4
ALE/RIS						
Sarioglu 2006	57.3/60.3	70 mg QW/5 mg QD	50	1	12.1/14.7	1
Rosen 2005	64.2/64.8	70 mg QW/35 mg QW	1053	1	18.3/18.7	1,2

Continued

Table 1 (Continued). Key features of included studies.

Trial	Mean age (yrs)	Dosage*	Sample size	Follow-up (yrs)	Years after menopausal (yrs)	Out-come#
ALE/RLX						
Sambrook 2004	61.5/61.8	70 mg QW/60 mg QD	487	1	14.5/14.9	1,2
Luchey 2004	63.8/64.7	70 mg QW/60 mg QD	456	1	17.3/17.8	1,2
Recker 2007	65.7/65.5	10 mg QD/60 mg QD	1423	2	19.0/18.5	3,4
Iwamoto 2008	70.3/68.5	5 mg QD/60 mg QD	122	1	NS	1,3
ALE/TPD						
Body 2002	65/66	10 mg QD/40 ug QD	146	2	19/18	1,2,4
Finkelstein 2010	64/65	10 mg QD/40 ug QD	49	3	NS	1
ALE/ZOL						
Tan 2016	68/68.1	70 mg QD/5 mg QY	105	3	NS	1,2
CT/PLA						
Chesnut 2000	68.2/68.2	100–400 IU QD	1254	5	23/22	1,3,4
Reginster 1995	53.2/53	50–200 IU QD	251	2	3.0/2.7	1
Binkley 2012	66.5/66.5	0.2 mg QD	367	1	NS	1,2
Binkley 2014	67.5/66.6	0.2 mg QD	129	1	NS	1
Henriksen 2016	66.5/67	0.8 mg QD	4665	3	NS	1,2,3,4
Overgaard 1994	52/52	100–400 IU QD	134	2	NS	1
CT/TPD						
Zhang 2012	63.3/64.3	200 IU QD/20 ug QD	124	1	13.5/14.7	1
Li 2013	65/65.1	200 IU QD/20 ug QD	453	1.5	NS	1
DEN/IBA						
Recknor 2013	67.2/66.2	60 mg Q6M/150 mg QM	833	1	20.4/19.7	1,2,3,4
DEN/PLA						
Bone 2011	59.4/58.9	60 mg Q6M	256	4	10.3/9.4	1,2
Nakamura 2012	65.1/64.6	14–100 mg QD	212	2	15.6/5.6	1,2
Bone 2008	59.8/58.9	60 mg Q6M	332	2	NS	1,2,3,4
Cummings 2009	72.3/72.3	60 mg Q6M	7808	3	NS	1,2,3,4
DEN/RIS						
Roux 2014	67.8/67.7	60 mg Q6M/150 mg QM	870	1	20.2/20.1	1,2
DEN/TPD						
Tsai 2013	66.3/65.5	60 mg Q6M/20 ug QD	94	1	NS	1,2

Continued

Table I (Continued). Key features of included studies.

Trial	Mean age (yrs)	Dosage*	Sample size	Follow-up (yrs)	Years after menopausal (yrs)	Out-come#
DEN/ZOL						
Miller 2016'	68.5/69.5	60 mg Q6M/5 mg QY	643	1	20.8/19.9	1,2
Anastasilakis 2015	63/63	60 mg Q6M/5 mg QY	58	1	NS	1
IBA/PLA						
Chesnut 2004	69/69	2.5 mg QD	2946	3	20.9/20.8	3,4
Stakkestad 2003	54.8/54.6	0.5–2 mg Q3M	629	1	4.3/4.1	1,2
Mcclung 2009	53.7/53.4	150 mg QM	160	1	5.3/5.5	1,2
Mcclung 2004	58.2/57.9	0.5–2.5 mg QD	653	2	9/8.2	1,2
Lester 2012	NS	150 mg QM	50	5	NS	1
Lewiecki 2009	64.8/63.5	150 mg QM	93	1	NS	1,2
Ravn 1996	65.2/63.9	0.5–5 mg QD	180	1	NS	1
RIS/PLA						
Valimaiki 2007	66.1/65.4	5 mg QD	170	2	17.7/19.5	1
Fogelman 2000	65/64	2.5–5 mg QD	541	2	18/17	1,3
Clemmesen 1997	67/70	2.5 mg QD	88	3	20/23	1,3,4
Harris 1999	68/69	2.5–5 mg QD	2468	3	24/24	1,3,4
Reginster 2000	71/71	2.5–5 mg QD	1226	3	25/25	1,3,4
Mcclung 2001	74/74	2.5–5 mg QD	5445	3	28/28	4
Hooper 2005	53/52.6	2.5–5 mg QD	383	3	3.62/3.88	1,3,4
Mortensen 1998	52.1/51.2	5 mg QD	111	2	3/3	1,3,4
Li 2005	NS	5 mg QD	60	1	NS	1
Palomba 2008	52.3/51.4	35 mg QW	81	3	NS	3,4
Siris 2008	64/64	5 mg QD	620	3	NS	3,4
RIS/STR						
Narula 2012	55.6/57.7	35 mg QW/2 g QD	190	1	NS	1,2
RIS/TPD						
Anastasilakis 2008	64.7/65.4	35 mg QW/20 ug QD	44	1	16.1/19.2	1
Kendler 2017	71.6/72.6	35 mg QW/20 ug QD	1360	2	NS	3,4
RLX/PLA						
Zheng 2003	59.5/59.4	60 mg QD	204	1	10.3/10.0	1
Miller 2008	57.86/57.7	60 mg QD	564	2	10.69/11.15	1,2
Meunier 1999	60.2/59.2	60–150 mg QD	129	2	11.7/12.7	1,2
Morii 2003	65.2/64.3	60–120 mg QD	280	1	15.2/14.4	1,3,4
Liu 2004	65.5/65.1	60 mg QD	204	1	17.3/16.4	1,2
Ettinger 1999	65/65	60–120 mg QD	6828	3	17/18	3,4

Continued

Table I (Continued). Key features of included studies.

Trial	Mean age (yrs)	Dosage*	Sample size	Follow-up (yrs)	Years after menopausal (yrs)	Out-come#
RLX/PLA (continued)						
Silverman 2008	66.4/66.5	60 mg QD	3734	3	19.5/19.5	3,4
Lufkin 1998	68.2/68.2	60–80 mg QD	143	1	22.0/22.2	1,2,3,4
Delmas 1997	55/55	30–150 mg QD	601	2	5/4	1
Mcclung 2006	57.5/57.5	60 mg QD	246	2	9/8	1,2
Bueno 2017	NS	60 mg QD	2924	3	NS	3,4
Ensrud 2008	67.5/67.5	60 mg QD	10101	5	NS	3,4
STR/PLA						
Hwang 2008	64.3/65.8	2 g QD	125	1	16.2/18.2	1,2
Meunier 2002	66.7/65.6	0.5–2 g QD	353	2	17.5/19.1	3
Liu 2009	66.4/66.1	2 g QD	329	1	18.0/17.2	1,2
Meunier 2004	69.4/69.3	2 g QD	1649	3	22.1/21.6	3,4
Meunier 2009	69.4/69.3	2 g QD	1649	4	22.1/21.7	3
Reginster 2005	76.7/76.8	2 g QD	5091	5	28.4/28.5	3,4
Reginster 2008	76.7/76.8	2 g QD	5091	5	28.4/28.5	3,4
TPD/PLA						
Miyauchi 2010	69.2/70.4	20 ug QD	203	2	19.66/20.50	1,2
Neer 2001	69/69	20–40 ug QD	1637	1.9	21/21	3,4
Nakamura 2012'	75/75.4	56.5 ug QD	578	1.5	25.6/25.3	1,2,3,4
Krege 2012	NS	20 ug QD	1085	1.8	NS	4
TPD/ZOL						
Cosman 2011	63.8/66.1	20 ug QD/5 mg QY	275	1	NS	1,2,3,4
ZOL/PLA						
Mcclung 2009'	184/186	5 mg QY	400	2	11.5/11.4	1,2
Bai 2013	56.5/57.1	5 mg QY	483	2	NS	3,4
Black 2007	NS	5 mg QY	7765	3	NS	3,4
Chao 2013	54.6/55.3	5mg QY	660	3	NS	3,4
Grey 2009	65/62	5 mg QY	50	2	NS	1,2
Grey 2014	65/65	1–5mg QY	172	2	NS	1
Hwang 2011	72.5/73.3	5 mg QY	323	3	NS	2,3,4

*Dosage: QD, once a day; QW, once a week; QM, once a month; QY, once a year; IU, International Unit
#Outcome: 1, lumbar spine BMD; 2, total hip BMD; 3, vertebral fracture; 4, non-vertebral fracture
NS, not specified

Table II. Summary WMD of percentage change in lumbar spine BMD from baseline to one year of treatment for each direct comparison.

Comparison	WMD (95 % CI)	P-heterogeneity	I-squared	Tau-squared
ABL/TPD	*1.48 (0.84, 2.12)*	–	–	–
ABL/PLA	*9.31 (8.62, 10.00)*	–	–	–
ALE/CT	*3.95 (3.14, 4.77)*	0.74	<0.01 %	<0.001
ALE/DEN	-0.20 (-1.59, 1.19)	–	–	–
ALE/IBA	0.38 (-0.32, 1.08)	0.6	<0.01 %	<0.001
ALE/PLA	*4.58 (4.14, 5.02)*	<0.00001	88 %	0.63
ALE/RIS	0.99 (-0.64, 2.62)	0.008	79 %	1.47
ALE/RLX	*2.86 (1.88, 3.85)*	0.11	56 %	0.4
ALE/TPD	*-5.28 (-10.93, 0.36)*	0.002	89 %	14.83
ALE/ZOL	*-8.08 (-10.60, -5.56)*	–	–	–
CT/PLA	0.37 (-2.05, 2.80)	<0.00001	98 %	13.05
CT/TPD	*-4.11 (-4.49, -3.73)*	0.61	<0.01 %	<0.001
DEN/IBA	*2.11 (1.56, 2.66)*	–	–	–
DEN/PLA	*5.32 (4.91, 5.73)*	0.31	16 %	0.04
DEN/RIS	*2.30 (1.76, 2.84)*	–	–	–
DEN/TPD	-0.70 (-2.67, 1.27)	–	–	–
DEN/ZOL	*2.03 (1.51, 2.55)*	0.16	48 %	0.98
IBA/PLA	*3.54 (2.78, 4.30)*	0.02	62 %	0.47
IBA/RIS	*2.51 (1.34, 3.68)*	–	–	–
RIS/PLA	*2.85 (2.07, 3.63)*	0.0003	75 %	0.80
RIS/STR	-2.31 (-5.99, 1.37)	–	–	–
RIS/TPD	*-2.69 (-4.26, -1.12)*	–	–	–
RLX/PLA	*2.26 (1.90, 2.62)*	0.08	46 %	0.23
STR/PLA	*5.13 (3.39, 6.87)*	0.06	71 %	1.12
TPD/PLA	*6.35 (3.77, 8.93)*	<0.00001	96 %	6.64
TPD/ZOL	*2.75 (1.56, 3.94)*	–	–	–
ZOL/PLA	*3.56 (2.19, 4.93)*	0.03	72 %	1.03

p-value less than 0.05 is considered as significance with italic fonts

Table III. Summary WMD of percentage change in total hip BMD from baseline to one year of treatment for each direct comparison.

Comparison	WMD (95 % CI)	P-heterogeneity	I-squared	Tau-squared
ABL/TPD	*1.10 (0.76, 1.44)*	–	–	–
ABL/PLA	*3.35 (3.02, 3.68)*	–	–	–
ALE/DEN	*-1.44 (-2.41, -0.47)*	–	–	–
ALE/IBA	0.14 (0.00, 0.28)	0.29	20 %	0.02
ALE/PLA	*2.39 (2.01, 2.77)*	<0.00001	78 %	0.22
ALE/RIS	*1.09 (0.69, 1.49)*	0.67	<0.01 %	<0.001
ALE/RLX	*1.21 (0.78, 1.64)*	0.21	36 %	0.05
ALE/TPD	*-2.41 (-3.97, -0.85)*	–	–	–
ALE/ZOL	*-3.70 (-4.22, -3.18)*	–	–	–
CT/PLA	*0.53 (0.32, 0.74)*	0.53	<0.01 %	<0.001
DEN/IBA	*1.18 (0.81, 1.55)*	–	–	–
DEN/PLA	*3.18 (2.91, 3.45)*	0.14	42 %	0.08
DEN/RIS	*1.56 (1.22, 1.90)*	–	–	–
DEN/TPD	*1.84 (0.41, 3.27)*	–	–	–
DEN/ZOL	*1.31 (0.90, 1.72)*	–	–	–
IBA/PLA	*1.83 (1.21, 2.44)*	0.02	70 %	0.25
IBA/RIS	*0.84 (-0.34, 2.02)*	–	–	–
RIS/STR	*-0.59 (-3.76, 2.58)*	–	–	–
RLX/PLA	*1.43 (0.93, 1.92)*	0.70	<0.01 %	<0.001
STR/PLA	*3.26 (2.62, 3.90)*	0.37	<0.01 %	<0.001
TPD/PLA	*2.31 (2.01, 2.61)*	0.55	<0.01 %	<0.001
TPD/ZOL	-1.08 (-1.93, -0.23)	–	–	–
ZOL/PLA	2.70 (2.28, 3.11)	0.64	<0.01 %	<0.001

p-value less than 0.05 is considered as significance with italic fonts

Table IV. Summary ORs of vertebral fracture for each direct comparison.

Comparison	WMD (95 % CI)	P-heterogeneity	I-squared	Tau-squared
ABL/PLA	*0.13 (0.05, 0.37)*	–	–	–
ABL/TPD	0.66 (0.19, 2.35)	–	–	–
ALE/IBA	1.02 (0.29, 3.53)	–	–	–
ALE/PLA	*0.53 (0.45, 0.63)*	0.99	<0.01 %	<0.001
ALE/RLX	1.33 (0.62, 2.82)	0.68	<0.01 %	<0.001
CT/PLA	0.79 (0.51, 1.24)	0.07	69	0.07
DEN/IBA	1.00 (0.14, 7.12)	–	–	–
DEN/PLA	*0.31 (0.24, 0.40)*	0.96	<0.01 %	<0.001
IBA/PLA	*0.46 (0.32, 0.67)*	–	–	–
RIS/PLA	*0.55 (0.45, 0.69)*	0.83	<0.01 %	<0.001
RIS/TPD	*2.38 (1.50, 3.77)*	–	–	–
RLX/PLA	*0.63 (0.54, 0.74)*	0.47	<0.01 %	<0.001
STR/PLA	*0.61 (0.51, 0.73)*	0.04	60 %	0.02
TPD/PLA	*0.26 (0.17, 0.37)*	0.53	<0.01 %	<0.001
TPD/ZOL	0.19 (0.02, 1.68)	–	–	–
ZOL/PLA	*0.30 (0.24, 0.37)*	0.38	2 %	<0.001

p-value less than 0.05 is considered as significance with italic fonts

Vertebral fracture

As presented in Table IV, nine drugs showed a significant decrease in vertebral fractures compared with PLA: ABL (OR = 0.13, 95% CrI = 0.05-0.37), ALE (0.53, 0.45-0.63), DEN (0.31, 0.24-0.40), IBA (0.46, 0.32-0.67), RIS (0.55, 0.45-0.69), RLX (0.63, 0.54-0.74), STR (0.61, 0.51-0.73), TPD (0.26, 0.17-0.37) and ZOL (0.30, 0.24-0.37). However, mutual comparisons of the ten drugs revealed that there was only one significant result which was that RIS was superior to TPD (2.38, 1.50-3.77).

Non-vertebral fracture

As presented in Table V, all significant results of the comparisons were from placebo-controlled trials: ABL (OR = 0.53, 0.30-0.95), ALE (0.78, 0.69-0.88), DEN (0.78, 0.66-0.93), RIS (0.69, 0.59-0.80), STR (0.86, 0.76-0.96), TPD (0.67, 0.52-0.87), and ZOL (0.69, 0.60-0.79).

Table V. Summary ORs of non-vertebral fracture for each direct comparison.

Comparison	WMD (95 % CI)	P-heterogeneity	I-squared	Tau-squared
ABL/TPD	0.74 (0.40, 1.37)	–	–	–
ABL/PLA	*0.53 (0.30, 0.95)*	–	–	–
ALE/IBA	0.87 (0.40, 1.89)	–	–	–
ALE/PLA	*0.78 (0.69, 0.88)*	0.08	45 %	0.03
ALE/RLX	0.91 (0.44, 1.91)	–	–	–
ALE/TPD	3.70 (0.98, 14.06)	–	–	–
CT/PLA	0.91 (0.70, 1.18)	0.98	<0.01 %	<0.001
DEN/IBA	1.13 (0.53, 2.40)	–	–	–
DEN/PLA	*0.78 (0.66, 0.93)*	0.19	41 %	0.23
IBA/PLA	0.89 (0.65, 1.22)	–	–	–
RIS/PLA	*0.69 (0.59, 0.80)*	0.13	38 %	0.06
RIS/TPD	1.53 (0.91, 2.57)	–	–	–
RLX/PLA	0.94 (0.86, 1.04)	0.63	<0.01 %	<0.001
STR/PLA	*0.86 (0.76, 0.96)*	0.89	<0.01 %	<0.001
TPD/PLA	*0.67 (0.52, 0.87)*	0.81	<0.01 %	<0.001
TPD/ZOL	0.87 (0.31, 2.46)	–	–	–
ZOL/PLA	*0.69 (0.60, 0.79)*	0.38	2 %	<0.001

p-value less than 0.05 is considered as significance with italic fonts

Results of Network Meta-Analysis

Lumbar spine BMD

Seventy-nine studies were included in the analysis of lumbar spine BMD. Figure 2a showed the network plot of eligible comparisons. As shown in Figure 3, patients treated with any of the ten drugs showed a significantly greater increase of lumbar spine BMD than those treated with PLA: ABL (WMD = 9.0, 95% CI = 6.7-11.0), ALE (4.4, 3.9-4.9), CT (1.8, 0.97-2.7), DEN (5.6, 4.7-6.5), IBA (3.9, 3.0-4.8), RIS (3.1, 2.3-3.8), RLX (2.0, 1.1-2.9), STR (5.2, 3.3-7.0), TPD (7.2, 6.3-8.2) and ZOL (4.8, 3.6-6.0). Apart from that, ABL was better than most of the other drugs such as: (4.6, 2.3-7.0) for ALE, (7.2, 4.8-9.6) for CT, (3.4, 0.95-5.8) for DEN, (5.1, 2.7-7.6) for IBA, (5.9, 3.5-8.4) for RIS, (7.0, 4.5-9.5) for RLX, (3.8, 0.89-6.8) for STR and (4.2, 1.7-6.8) for ZOL. Moreover, ALE was associated with a significant increase of BMD in the lumbar spine compared with CT (2.6, 1.6-3.5), RIS (1.3, 0.44-2.2) and RLX (2.4, 1.4-3.3). Furthermore, DEN performed better than ALE (1.2, 0.24-2.3), CT (3.8, 2.6-5.0), IBA (1.7, 0.55-2.9), RIS (2.6, 1.5-3.7) and RLX (3.6, 2.3-4.9). Both IBA and RIS performed better than CT (2.1, 0.86-3.3; 1.3, 0.12-2.4) and IBA was also better than RLX (1.9, 0.61-3.1). Furthermore, TPD showed greater efficacy than ALE (2.8, 1.8-3.9), CT (5.4, 4.3-6.6), DEN (1.6, 0.36-2.9), IBA (3.3, 2.0-4.6), RIS (4.2, 3.0-5.4), RLX (5.2, 3.9-6.6) and ZOL (2.5, 1.0-3.8). Both STR and ZOL were better than CT (3.4, 1.4-5.4; 3.0, 1.6-4.4), RIS (2.1, 0.2-4.1; 1.7, 0.37-3.1) and RLX (3.2, 1.1-5.2; 2.7, 1.3-4.3). As stated above, CT and RLX were inferior to the other drugs and there was no significant difference between the two drugs.

Total hip BMD

Forty-seven studies were included in the analysis of total hip BMD. Figure 2b showed the network plot of eligible comparisons. As shown in Figure 4, except for CT, the remaining nine drugs all showed significantly greater efficacy compared with PLA, ABL (WMD = 3.5, 95% CI = 2.3-4.8), ALE (2.2, 1.8-2.6), DEN (3.6, 3.0-4.1), IBA (1.9, 1.4-2.5), RIS (1.5, 0.61-2.4), RLX (1.3, 0.65-2.0), STR (3.2, 2.1-4.3), TPD (2.6, 1.9-3.3) and ZOL (3.4, 2.7-4.1). Apart from that, ABL outperformed ALE (1.3, 0.0054-2.6), CT (2.9, 1.3-4.5), IBA (1.6, 0.19-2.9), RIS (2.1, 0.52-3.6) and RLX (2.2, 0.80-3.6). In addition, ALE performed better than CT (1.6, 0.49-2.7) and RLX (0.91, 0.22-1.8). Meanwhile, DEN was better than ALE (1.4, 0.74-2.0), CT (2.9, 1.8-4.1), IBA (1.6, 0.91-2.3), RIS (2.1, 1.2-3.0), RLX (2.3, 1.4-3.1) and TPD (0.96, 0.12-1.8). IBA was better than CT (1.3, 0.17-2.5) and STR achieved a better performance than CT (2.6, 1.1-4.1), RIS (1.7, 0.37-3.1) and RLX (1.9, 0.61-3.2). Furthermore, TPD was better than CT (2.0, 0.72-3.2), RIS (1.1, 0.038-2.2) and RLX (1.3, 0.34-2.3) and ZOL was better than ALE (1.2, 0.49-1.9), CT (2.8, 1.6-4.0), IBA (1.5, 0.62-2.3), RIS (1.9, 0.89-3.0) and RLX (2.1, 1.2-3.0). Similar to lumbar spine BMD, the efficacy of CT was unsatisfactory, demonstrating its inferiority to ABL, ALE, DEN, IBA, STR, TPD, and ZOL.

Vertebral fracture

Forty-three studies were included in the analysis of vertebral fracture. Figure 2c showed the network plot of eligible comparisons. As shown in Figure 5, except for CT, the remaining nine drugs all showed a significantly lower risk of vertebral fracture compared with PLA: ABL (OR = 0.13, 95% CI = 0.04-0.34), ALE (0.55, 0.44-0.67), DEN (0.31, 0.22-0.43), IBA (0.46, 0.30-0.69), RIS (0.55, 0.43-0.69), RLX (0.62, 0.51-0.75), STR (0.62, 0.53-0.72), TPD (0.23, 0.17-0.32) and ZOL (0.32, 0.25-0.44). Apart from that, patients treated with ABL were significantly better than those treated with ALE (0.23, 0.072-0.65), CT (0.16, 0.047-0.44), IBA (0.28, 0.082-0.83), RIS (0.23, 0.071-0.64), RLX (0.21, 0.063-0.54) and STR (0.21, 0.064-0.56). ALL, ALE, IBA and RIS were better than CT (0.66, 0.47-0.95; 0.56, 0.34-0.93; 0.67, 0.46-0.97, respectively). Furthermore, DEN was superior to ALE (0.57, 0.38-0.83), CT (0.38, 0.24-0.59), RIS (0.56, 0.37-0.85), RLX (0.50, 0.34-0.73) and STR (0.50, 0.35-0.72). In addition, TPD was more effective than ALE (0.43, 0.28-0.63), CT (0.28, 0.18-0.44), IBA (0.51, 0.30-0.86), RIS (0.42, 0.30-0.60), RLX (0.38, 0.25-0.55) and STR (0.38, 0.26-0.54). Besides, ZOL have more curative effects than ALE (0.59, 0.42-0.85), CT (0.39, 0.27-0.61), RIS (0.59, 0.41-0.88), RLX (0.52, 0.38-0.76) and STR (0.52, 0.38-0.75).

Non-vertebral fracture

Forty-four studies were included in the analysis of non-vertebral fracture. Figure 2d showed the network plot of eligible comparisons. As shown in Figure 6**,** there were six drugs with a significantly lower risk of non-vertebral fracture compared with PLA, including ABL (OR = 0.49, 95% CI = 0.27-0.83), ALE (0.78, 0.68-0.89), DEN (0.80, 0.64-0.98), RIS (0.69, 0.58-0.81), TPD (0.60, 0.47-0.77) and ZOL (0.67, 0.56-0.80). Apart from that, ABL was superior to CT (0.54, 0.28-0.98), RLX (0.53, 0.29-0.90) and STR (0.58, 0.31-0.98).

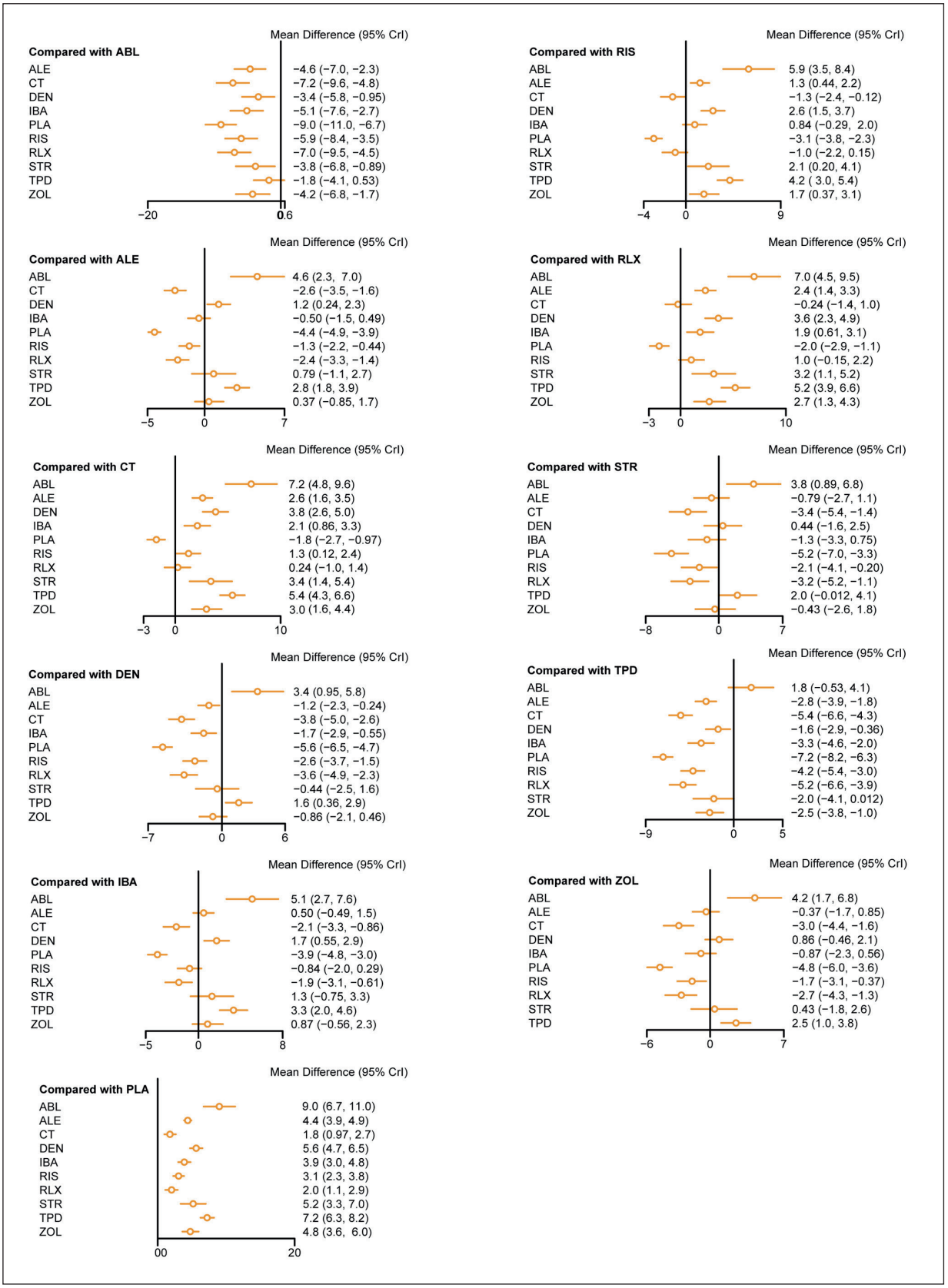

Figure 3. Forest plot of Lumbar spine BMD.

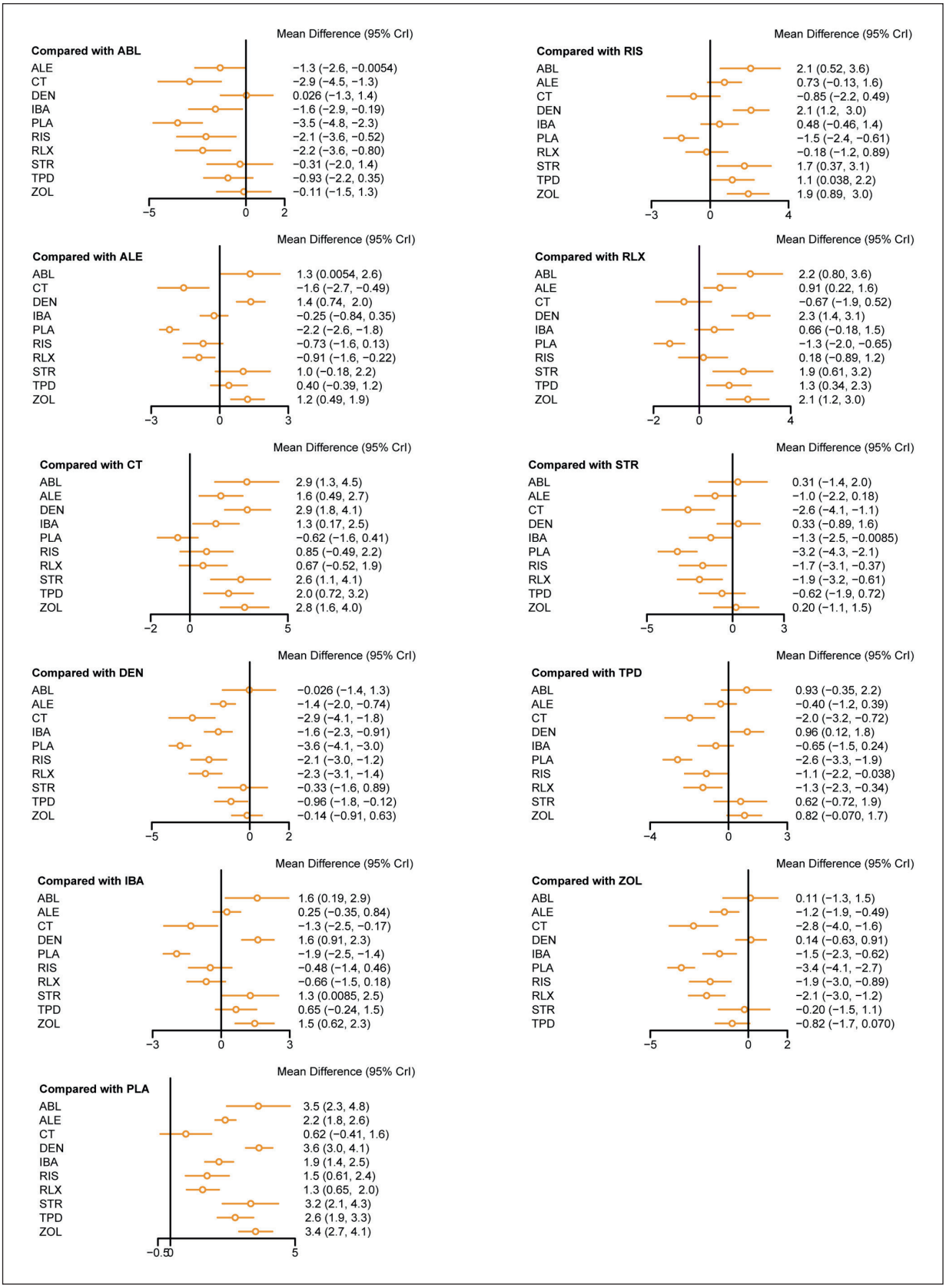

Figure 4. Forest plot of Total hip BMD.

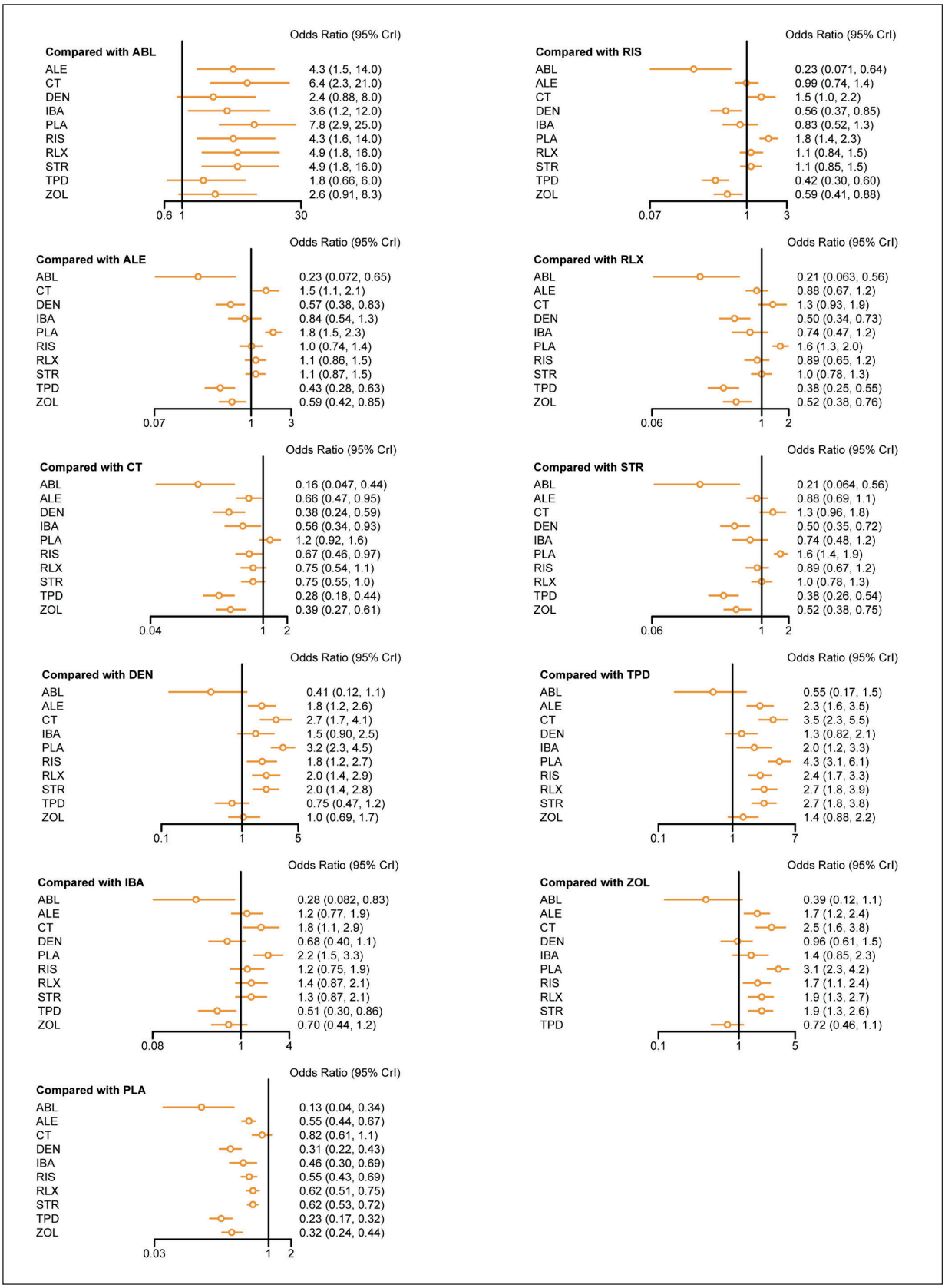

Figure 5. Forest plot of Vertebral fracture.

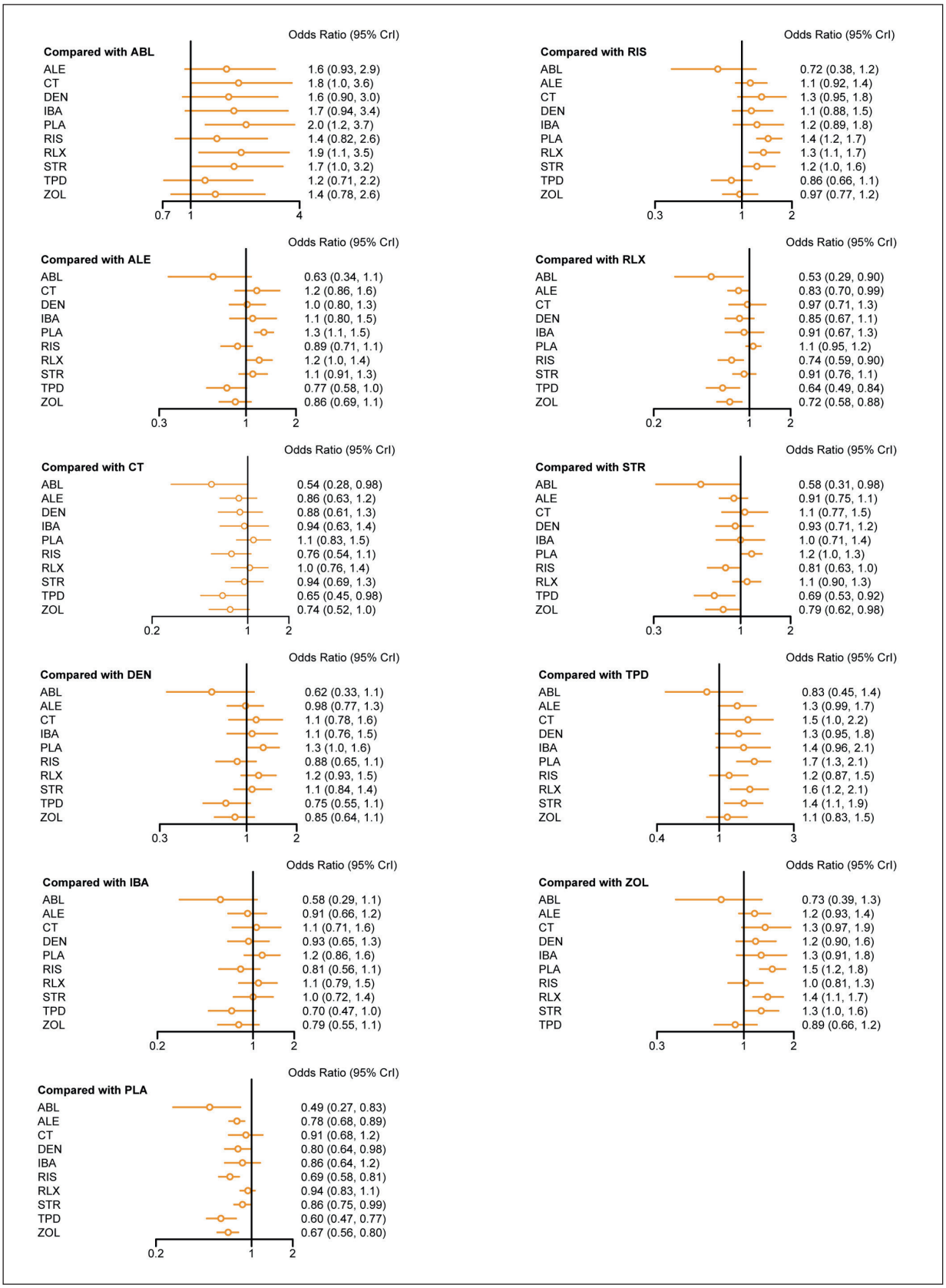

Figure 6. Forest plot of Non-vertebral fracture.

Table VI. SUCRA values of all studied interventions with regard to lumbar spine BMD, total hip BMD, VF, and NVF.

Outcomes	ABL	ALE	CT	DEN	IBA	PLA	RIS	RLX	STR	TPD	ZOL
Lumbar spine BMD	98.5%	53.3%	13.6%	75.8%	43.0%	0.0%	30.6%	16.8%	66.0%	90.2%	60.2%
Total hip BMD	85.7%	49.5%	11.4%	87.5%	41.2%	1.1%	27.2%	23.0%	78.9%	60.4%	83.9%
VF	97.3%	43.8%	10.4%	76.1%	54.6%	0.8%	42.5%	29.4%	28.8%	89.2%	75.2%
NVF	93.1%	53.3%	23.4%	46.2%	41.4%	5.8%	69.1%	19.1%	33.4%	88.7%	73.6%

Furthermore, ALE and RIS were more effective than RLX (0.83, 0.70-0.99; 0.74, 0.59-0.90). In addition, both TPD and ZOL were associated with a lower risk of non-vertebral fracture than RLX (0.64, 0.49-0.84; 0.72, 0.58-0.88, respectively) and STR (0.69, 0.53-0.92; 0.79, 0.62-0.98, respectively).

Rank of Treatments

The corresponding rank of eleven interventions including PLA was presented based on their SUCRA value. For the four outcomes (lumbar spine BMD, total hip BMD, VF, and NVF) of the analysis, the best treatments were ABL (98.5%), DEN (87.5%), ABL (97.3%), and ABL (93.1%), respectively. The full details of all four ranks were presented in Table VI and Figure 7.

Consistency

The node-splitting method was used to assess the consistency of direct and indirect evidence (Figures 8, 9, 10, and 11). The evidence between direct and indirect comparisons appeared to be consistent if the p-value was > 0.05. For the results of lumbar spine BMD, the overall consistency was satisfactory except for the comparison between ZOL and ALE. For the results of total hip BMD, inconsistency occurred in three group comparisons (TPD and ALE, ZOL and ALE, ZOL and DEN). For the results of vertebral fracture and non-vertebral fracture, all the groups met the criteria of consistency with p-values > 0.05.

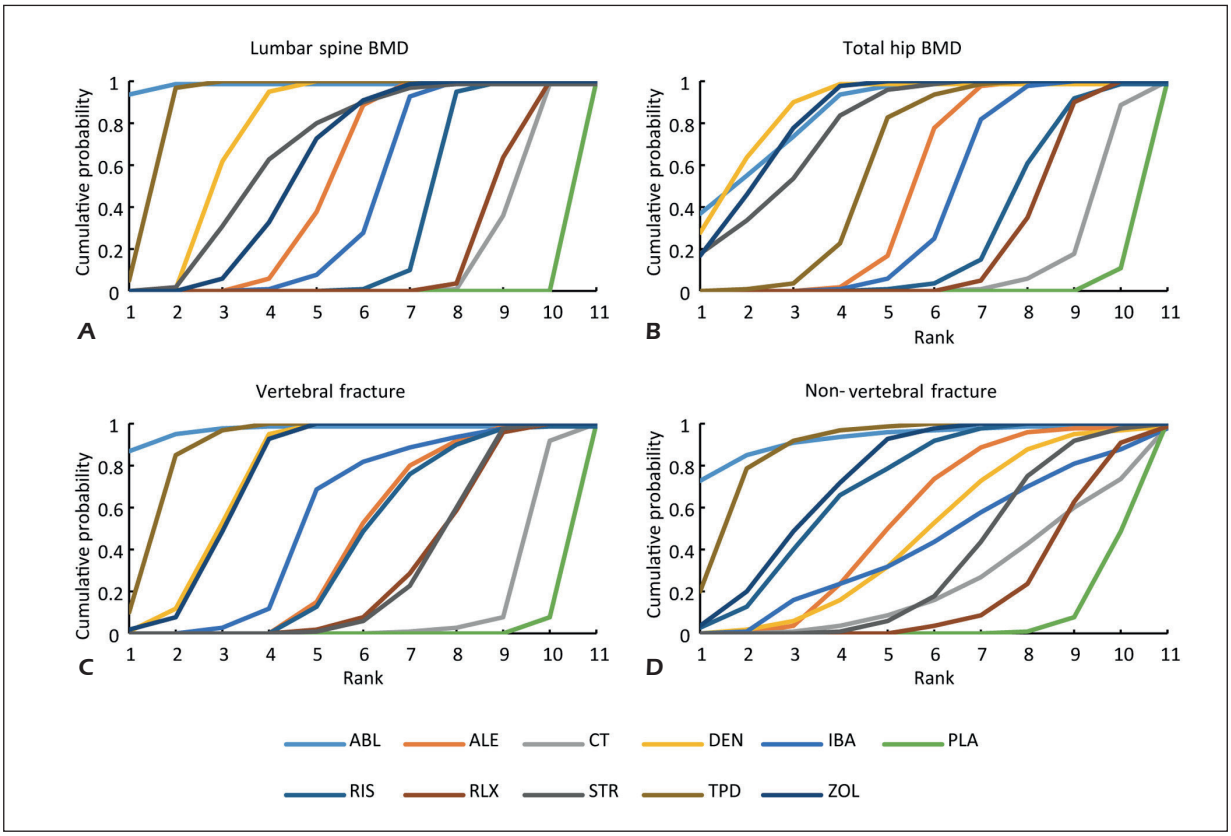

Figure 7. Ranking graph of **A**, Lumbar spine BMD, **B**, Total hip BMD, **C**, Vertebral fracture, and **D**, Non-vertebral fracture.

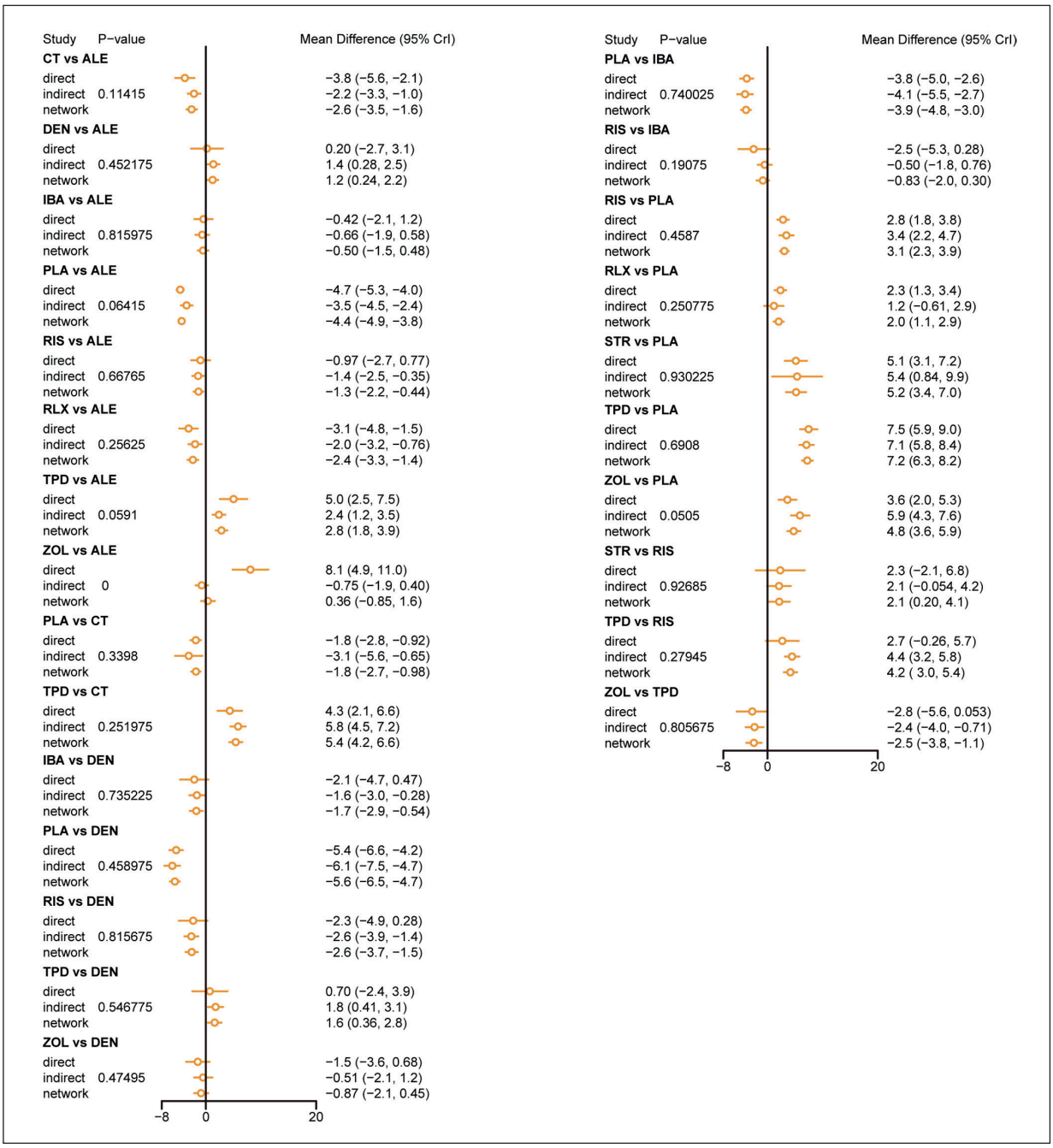

Figure 8. Comparison of Lumbar Spine BMD between direct and indirect evidence.

Publication Bias and Quality of Included Studies

Funnel plots were depicted to assess publication bias (Figure 12). Each dot represented a study, and the conclusion regarding publication bias was drawn based on the asymmetrical distribution of dots. As a result, no significant publication bias was observed in the four funnel plots of outcomes. The studies included in this network meta-analysis were assessed based on the Modified JADAD Scale. The full mark was 7, which comprised blinding techniques (0–2), randomization (0–2), concealment allocation (0–2) and disclosure of withdrawals (0–1). The results of the Modified JADAD Scale of all 105 studies were presented in Table VII.

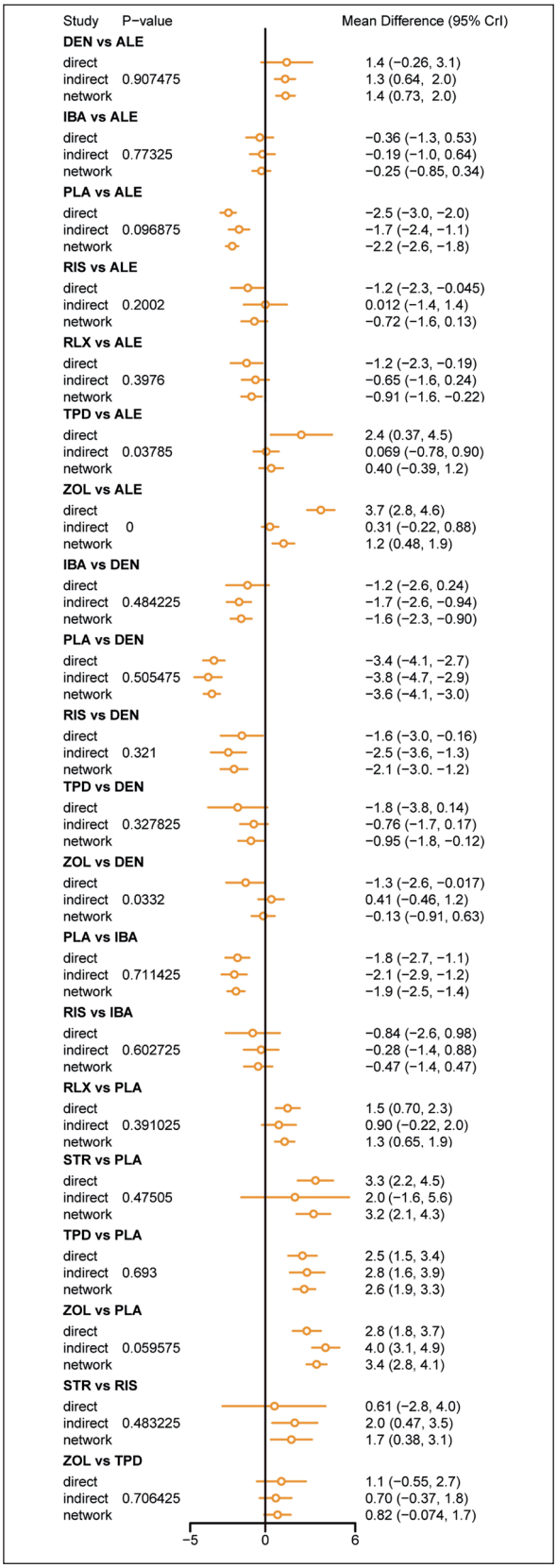

Figure 9. Comparison of Total hip BMD between direct and indirect evidence.

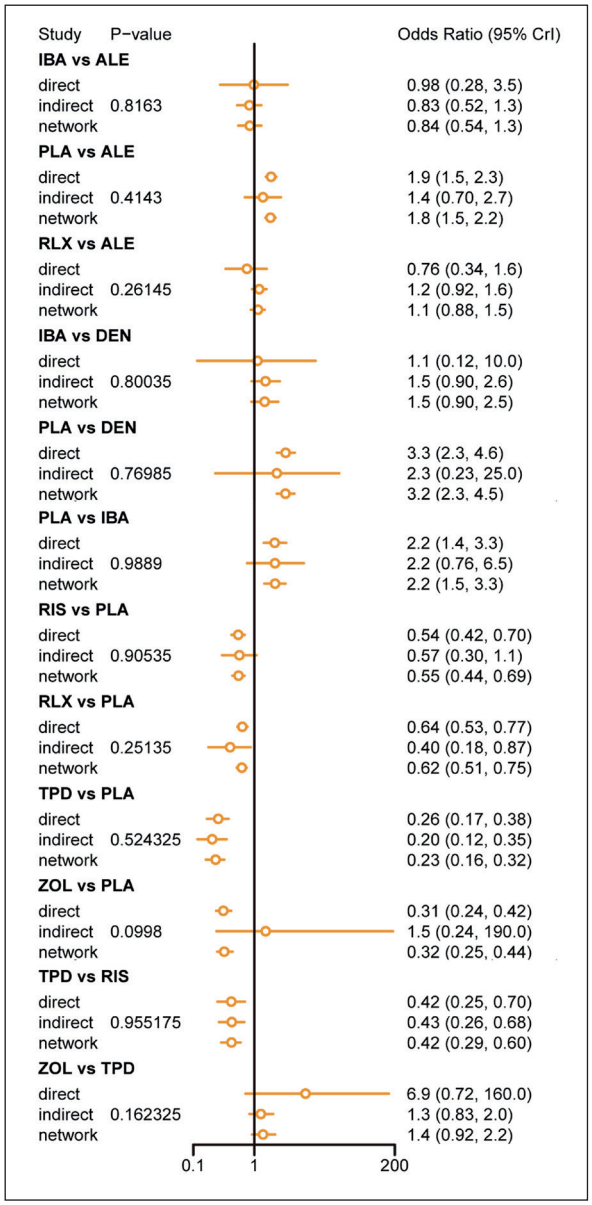

Figure 10. Comparison of Vertebral fracture between direct and indirect evidence.

Discussion

In this NMA, we systematically assessed the efficacy of ABL, ALE, CT, DEN, IBA, RIS, RLX, STR, TPD, and ZOL in increasing BMD and reducing fracture rate. A total of 122, 685 cases from 103 studies were included. As shown in our assessment, ABL was considered as the best therapy for the treatment of postmenopausal women with osteoporosis because it ranked first in the outcomes of lumbar spine BMD, VF, and NVF based on the SUCRA value and second in the outcome of total hip BMD. Similar to the

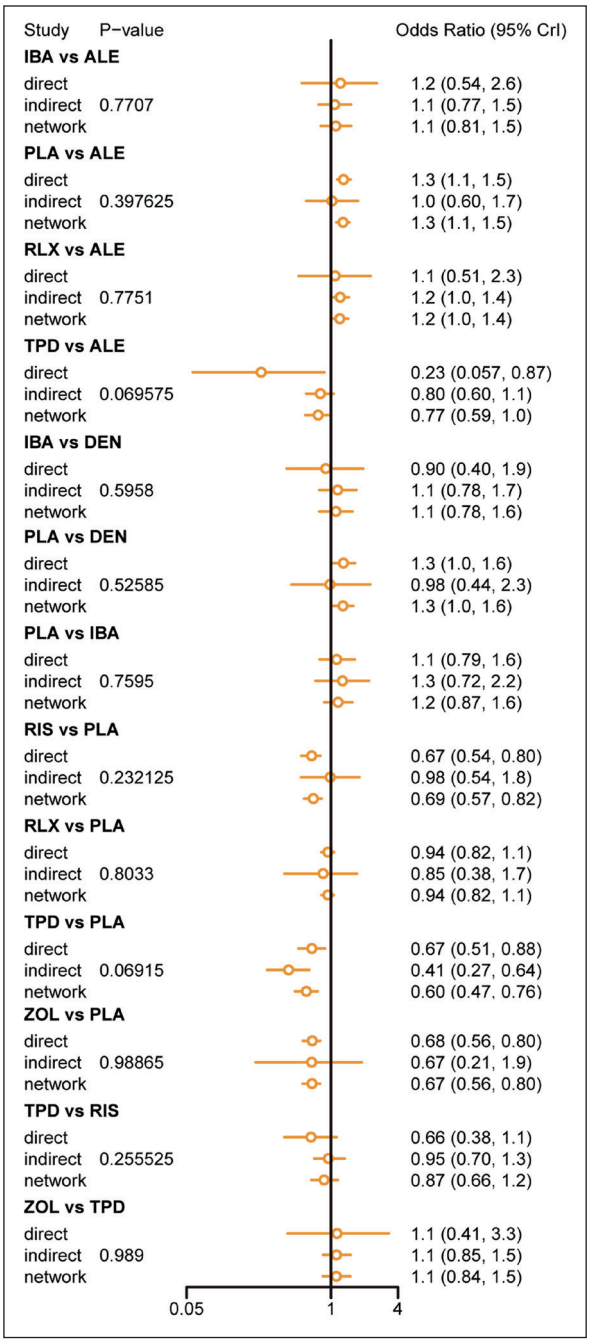

Figure 11. Comparison of Non-vertebral fracture between direct and indirect evidence.

related drug TPD, ABL was also a parathyroid hormone-related protein analog drug applied to treat osteoporosis, which successfully completed a Phase III trial in 2016[7]. It has 41% homology to parathyroid hormone (PTH1-34) and 76% homology to parathyroid hormone-related protein[117]. It works as an anabolic agent for bone, selectively activated by the parathyroid hormone 1 receptor of osteoblasts and osteocytes[118,119]. On 28 April 2017, it was approved by the USA food and drug administration for the treatment of postmenopausal osteoporosis. As a result, ABL may become a new standard for the treatment of postmenopausal women with osteoporosis. Furthermore, for the outcome of total hip BMD, DEN achieved the highest SUCRA value, indicating that DEN was the best drug to improve the total hip BMD. DEN is a human monoclonal antibody and a RANKL inhibitor, which prevents the development of osteoclasts and inhibits bone resorption[120]. For patients with evidently low total hip BMD, DEN may be a more suitable drug available for them. In addition, DEN had good efficacy in other aspects, ranking third, third and sixth in the outcomes of lumbar spine BMD, VF, and NVF, respectively. TPD was still efficient enough to be a fine choice, ranked just behind ABL in the outcomes of lumbar spine BMD, VF, and NVF. However, the performances of CT and RLX were not satisfactory. CT performed worst in the outcomes of lumbar spine BMD, total hip BMD, and VF and ranked the last but one in the outcome of NVF among ten drugs. Meanwhile, RLX ranked the lowest in the outcome of NVF, the third to last in the outcome of VF, and last but one in the outcomes of lumbar spine BMD and total hip BMD. The primary function of CT is to reduce blood calcium, opposing the effects of parathyroid hormone[121] and RLX is a selective estrogen receptor modulator that can function analogously to estrogen to prevent postmenopausal osteoporosis[122]. The remaining five drugs all had medium efficacy in the treatment parameters, including four bisphosphonates (ALE, IBA, RIS, and ZOL) and STR. Bisphosphonates are the most common drug used for osteoporosis, especially ALE, which can prevent bone loss and reduce fracture rate[123]. STR is a strontium salt of ranelic acid that has both anti-resorptive and anabolic effects[124].

To our knowledge, this was the very largest NMA with respect to the effect of therapies for postmenopausal osteoporosis on BMD in the lumbar spine and fracture rate. A large number of studies and cases were included in this NMA. Furthermore, both direct and indirect comparisons were applied to achieve convincing results. Our results were consistent with previous studies. For instance, as the meta-analysis conducted by Wang et al[125] demonstrated, TPD is more effective than ALE in improving lumbar spine BMD. Moreover, a meta-analysis performed by Lin et al[126] suggested that DEN is more effective in in-

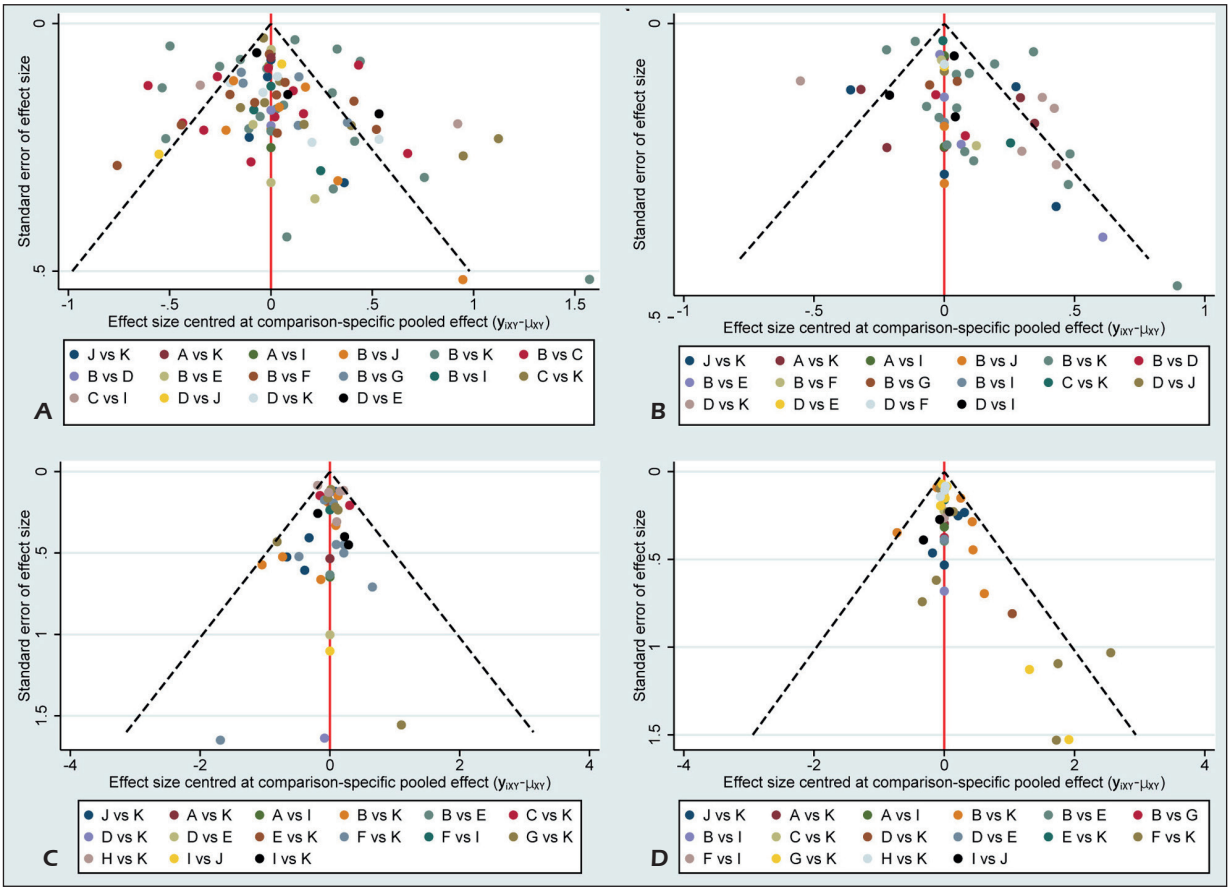

Figure 12. Funnel plots assessing publication bias. Asymmetry patterns indicate the presence of potential significant publication bias. **A**, Lumbar spine BMD, **B**, Total hip BMD, **C**, Vertebral fracture, and **D**, Non-vertebral fracture; (A) Abaloparatide, (B) Alendronate, (C) Calcitonin, (D) Denosumab, (E) Ibandronate, (F) Risedronate, (G) Raloxifene, (H) Strontium Ranelate, (I) Teriparatide, (J) Zoledronate, and (K) Placebo.

creasing BMD in the lumbar spine and total hip of postmenopausal women compared to ALE. Similar results were also found in the meta-analysis performed by Zhang et al[127], indicating that TPD and DEN perform better than ALE and RIS in the reduction of risk of VF. In the NMA undertaken by Reginster et al[128], ABL proved superior to DEN and TPD in reducing the risk of VF and NVF. However, there still remain some limitations in our NMA. As mentioned above, some inconsistency remained in the groups including ZOL *vs.* ALE in lumbar spine BMD, and TPD *vs.* ALE, ZOL *vs.* ALE and ZOL *vs.* DEN in total hip BMD. It may be explained that only one trial reporting the direct comparison between ZOL and ALE, with only 105 participants involved[109]. As a result, the corresponding results should be interpreted with caution and a clinical trial with a large sample size is suggested. In addition, another limitation is that the mode of administration is not uniform. For example, for the same ALE, some patients were instructed to take 10 mg once a day and some to take 70 mg once a week or even 150 mg once a month. It may contribute to the increased heterogeneity among studies due to the difference in compliance of participants and drug dosage. Therefore, further researches are needed to illuminate the influence of the mode of administration.

Conclusions

This network meta-analysis demonstrated that ABL can be considered as the preferable drug for improving BMD and reducing the risk of fracture. DEN and TPD are also quite effective, and in particular, DEN performs best in improving total BMD. Nevertheless, more high-quality RCTs are necessary to support and update our conclusions.

Table VII. Modified Jadad Scale.

Studies	Blinding	Randomization	Concealment allocation	Withdrawal	Total scores
ABL/TPD/PLA					
Miller 2016	2	0	2	1	5
ALE/CT/PLA					
Adami 1993	2	2	1	0	5
Downs 2000	2	1	2	0	5
Dursun 2001	0	1	0	0	1
ALE/DEN/PLA					
Lewiecki 2007	2	2	1	1	6
ALE/IBA/RIS					
Paggiosi 2014	0	1	2	1	4
ALE/IBA					
Guanabens 2013	0	2	2	1	5
Miller 2008'	1	1	1	1	4
ALE/PLA					
Black 1996	2	2	2	1	7
Bone 1997	1	1	0	0	2
Chesnut 1995	1	2	2	1	6
Cummings 1998	2	2	2	1	7
Devogelaer 1996	2	2	2	0	6
Hochberg 2005	2	1	0	0	3
Hosking 1998	2	1	2	0	5
Lau 2000	1	1	2	1	5
Liberman 1995	1	1	0	1	3
Pols 1999	2	1	1	0	4
Quandt 2005	2	1	1	0	4
Ravn 1999	0	1	0	0	1
Rossini 2001	0	1	0	0	1
Stpan 1999	2	1	2	0	5
Tucci 1996	2	1	2	0	5
Yan 2009	2	1	0	1	4
Yen 2000	1	2	2	1	6
ALE/RIS					
Rosen 2005	2	2	2	1	7
Sarioglu 2006	0	1	1	0	2
ALE/RLX					
Luchey 2004	2	2	2	1	7
Iwamoto 2008	0	1	0	1	2
Recker 2007	2	2	2	1	7
Sambrook 2004	2	2	2	1	7
ALE/TPD					
Body 2002	2	1	0	1	4
Finkelstein 2010	0	2	2	1	5
ALE/ZOL					
Tan 2016	2	2	2	1	7
CT/PLA					
Binkley 2012	2	1	2	1	6
Binkley 2014	2	1	0	1	4
Chesnut 2000	2	2	2	1	7
Henriksen 2016	2	2	2	1	7
Overgaard 1994	2	2	2	0	6
Reginster 1995	1	1	1	1	4
CT/TPD					
Li 2013	0	1	0	1	2
Zhang 2012	0	1	0	0	1
DEN/IBA					
Recknor 2013	0	2	2	1	5

Continued

Table VII (Continued). Modified Jadad Scale.

Studies	Blinding	Randomization	Concealment allocation	Withdrawal	Total scores
DEN/PLA					
Bone 2008	2	1	0	1	4
Bone 2011	2	2	1	1	6
Cummings 2009	0	1	0	1	2
Nakamura 2012	1	1	1	1	4
DEN/RIS					
Roux 2014	0	1	1	1	3
DEN/TPD					
Tsai 2013	2	2	2	1	7
DEN/ZOL					
Miller 2016'	2	1	1	1	5
Anastasilakis 2015	0	2	2	1	5
IBA/PLA					
Chesnut 2004	2	2	2	0	6
Lester 2012	1	1	0	1	3
Lewiecki 2009	1	1	0	1	3
Mcclung 2004	2	1	2	1	6
Mcclung 2009	2	1	0	0	3
Ravn 1996	2	1	1	1	5
Stakkestad 2003	2	1	2	1	6
RIS/PLA					
Clemmesen 1997	1	1	0	0	2
Fogelman 2000	1	1	1	1	4
Harris 1999	2	2	2	1	7
Hooper 2005	2	2	2	1	7
Li 2005	2	1	0	1	4
Mcclung 2001	2	1	1	0	4
Mortensen 1998	2	1	2	0	5
Palomba 2008	1	2	2	1	6
Reginster 2000	1	1	1	1	4
Siris 2008	1	1	0	0	2
Valimaiki 2007	1	2	1	0	4
RIS/STR					
Narula 2012	0	1	1	0	2
RIS/TPD					
Anastasilakis 2008	0	1	0	1	2
Kendler 2017	2	2	2	1	7
RLX/PLA					
Bueno 2017	1	2	2	0	5
Delmas 1997	2	1	2	0	5
Ensrud 2008	2	1	2	0	5
Ettinger 1999	2	2	2	1	7
Liu 2004	2	1	1	1	5
Lufkin 1998	1	1	2	1	5
Mcclung 2006	2	1	0	0	3
Meunier 1999	1	1	1	0	3
Miller 2008	2	2	2	1	7
Morii 2003	2	2	2	1	7
Silverman 2008	1	1	1	1	4
Zheng 2003	1	1	1	1	4
STR/PLA					
Hwang 2008	2	1	0	0	3
Liu 2009	1	1	1	1	4
Meunier 2002	2	1	2	1	6
Meunier 2004	1	1	0	1	3
Meunier 2009	2	1	0	1	4
Reginster 2005	1	1	1	1	4
Reginster 2008	1	1	1	1	4

Continued

Table VII (Continued). Modified Jadad Scale.

Studies	Blinding	Randomization	Concealment allocation	Withdrawal	Total scores
TPD/PLA					
Krege 2012	1	1	0	0	2
Miyauchi 2010	1	1	2	1	5
Nakamura 2012'	2	2	1	1	6
Neer 2001	0	1	1	0	2
TPD/ZOL					
Cosman 2011	2	2	2	1	7
ZOL/PLA					
Bai 2013	1	1	0	0	2
Black 2007	2	2	1	1	6
Chao 2013	1	1	0	0	2
Grey 2009	2	2	2	1	7
Grey 2014	2	2	2	1	7
Hwang 2011	1	1	0	0	2
Mcclung 2009'	2	2	2	0	6

Conflict of Interests

The authors declare that they have no conflict of interest.

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