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Pharmacological Therapies for Osteoporosis: A Bayesian Network Meta-Analysis

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Background: Numerous randomized controlled trials (RCTs) have evaluated pharmacological therapies for osteoporosis. The aim of this Bayesian network meta-analysis was to compare the efficacy and safety of pharmacological therapies for osteoporosis patients.

Material/Methods: The electronic databases of PubMed, Embase, and Cochrane Library were systematically searched for eligible RCTs from their inception up to January 2021. The primary endpoints were all fractures, vertebral fractures, and non-vertebral fractures, while the secondary endpoints were fractures at hip or peripheral locations, bone mineral density (BMD) at various sites, and potential adverse events.

Results: We included 79 RCTs reporting a total of 108 797 individuals in the final quantitative analysis. The results of network analysis indicated that romosozumab (92.1%) was the most effective in reducing the risk for all fractures, with the best therapeutic effects on vertebral fracture (97.2%) and non-vertebral fracture (88.0%). Romosozumab (92.5%) provided better therapeutic effects for the reduction of hip fracture. The best treatment agents for improving whole-body BMD (100.0%), spine BMD (95.7%), hip BMD (92.4%), femoral neck BMD (86.7%), and trochanter BMD (95.5%) were alendronate, strontium ranelate, ibandronate, risedronate, and ibandronate, respectively. Finally, the use of bazedoxifene was associated with the highest incidence of any upper-gastrointestinal event, nasopharyngitis, and back pain, while risedronate was associated with higher incidence of abdominal pain and dyspepsia.

Conclusions: This study found that romosozumab yielded the best effects for preventing fracture risk, while abaloparatide was the most effective in reducing the risk of vertebral fracture and non-vertebral fracture.

Keywords: Bone Density • Fractures, Bone • Network Meta-Analysis • Pharmacological and Toxicological Phenomena

Abbreviations: **BMD** – bone mineral density; **RCT** – randomized controlled trial; **SUCRA** – surface under the cumulative ranking

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Background

Osteoporosis is a chronic metabolic bone disease that is highly prevalent in the elderly population, especially in postmenopausal women [1]. Osteoporosis morbidity is rapidly increasing with the increase in the aging population, with an estimated 200 million people affected worldwide [2]. Changes in bone mineral density (BMD) in postmenopausal women are significantly associated with hormonal changes related to ovarian function after menopause [3]. Moreover, nearly half of women and one-third of men with osteoporosis present with bone fractures during their lives [4]. The crude estimated prevalence of osteoporotic fractures is 9 million worldwide, which has a direct impact on morbidity, mortality, quality of life, and treatment cost [5]. Although numerous pharmacological therapies remain to be developed for reducing the risk of fractures, fractures mainly occur in individuals with osteoporosis who are receiving treatment but show inadequate responses to therapy.

Currently, bisphosphonates are widely used to prevent and treat osteoporosis; however, the long-term use of bisphosphonates can induce bone micro-damage accumulation, excessive acceleration of mineralization, and atypical insufficiency fractures in the skeletal system [6]. Several systematic reviews have been conducted to compare various drugs for treating osteoporosis [7-9]. Murad et al included 116 randomized controlled trials (RCTs) and found that teriparatide, bisphosphonates, and denosumab are the most effective agents for preventing fragility fracture risk, but the differences in effectiveness among the investigated drugs were not significant [7]. Freemantle et al suggested that osteoporotic patients who received denosumab, risedronate, and zoledronate have a significantly lower risk of non-vertebral and hip fractures, while alendronate, strontium ranelate, and teriparatide yield beneficial effects for non-vertebral fractures. Moreover, mixed comparison results indicated that denosumab was associated with a greater reduction in new vertebral fractures than strontium ranelate, raloxifene, alendronate, and risedronate [8]. Barrionuevo et al enrolled 107 RCTs and comprehensively examined the effectiveness of various agents on the risk of fragility fractures in postmenopausal women [9].

Recently, the effectiveness of various pharmacological therapies to reduce the risk of fractures and improve BMD at various sites in osteoporotic patients has been studied in numerous RCTs, and the therapeutic effects of these drugs should be re-evaluated and updated. Moreover, prior meta-analyses did not address safety outcomes [7-9]. Therefore, our study systematically analyzed the current existing treatment options for osteoporosis, and a Bayesian network meta-analysis was performed to summarize the evidence through direct and indirect comparisons of different pharmacological therapies.

Material and Methods

This network meta-analysis was registered in PROSPERO (CRD42020158203) [10] and was conducted and reported following the network meta-analysis version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA-NMA Checklist) [11].

Search Strategy and Selection Criteria

We identified the studies published in English through a systematic search of PubMed, Embase, and the Cochrane Library from inception to January 2021, using the following search terms: "osteoporosis," "therapeutic," and "random*." The details of the search strategy in PubMed are presented in the **Supplementary Material**. We also scrutinized the reference lists of all relevant reviews and those of the eligible publications. Moreover, ClinicalTrials.gov (US NIH) was searched to identify completed studies that have not yet published data. After the exclusion of duplicate studies, 2 investigators independently reviewed the titles and abstracts of the remaining articles according to predefined inclusion criteria. The inclusion criteria were the following: (1) Study design: RCT; (2) Participants: osteoporosis; (3) Intervention and control: abaloparatide, alendronate, alfacalcidol, bazedoxifene, calcitonin, calcitriol, denosumab, elcatonin, eldecalcitol, ibandronate, lasofoxifene, neridronate, raloxifene, risedronate, romosozumab, strontium ranelate, and zoledronate; and (4) Outcomes: all fracture, vertebral fracture, non-vertebral fracture; fractures at hip, or peripheral locations, whole-body BMD, BMD at the spine, hip, femoral neck, and trochanter; and any potential adverse events.

Data Collection and Quality Assessment

The data collected included the first author's surname, publication year, country, sample size, mean age, sex, interventions and controls, co-calcium, co-vitamin D, follow-up duration, and investigated outcomes. The Jadad scale was used to evaluate methodological quality, as it is quite comprehensive and has been validated for assessing the quality of RCTs in meta-analyses [12]. Data extraction and quality assessment were conducted independently by 2 authors. Information was examined and adjudicated independently by another author referring to the original studies.

Statistical Analyses

We initially performed a pairwise meta-analysis using a random-effects model because it is likely the most appropriate and conservative methodology to account for between-trial heterogeneity within each comparison [13]. We estimated the relative treatment effects of the competing interventions

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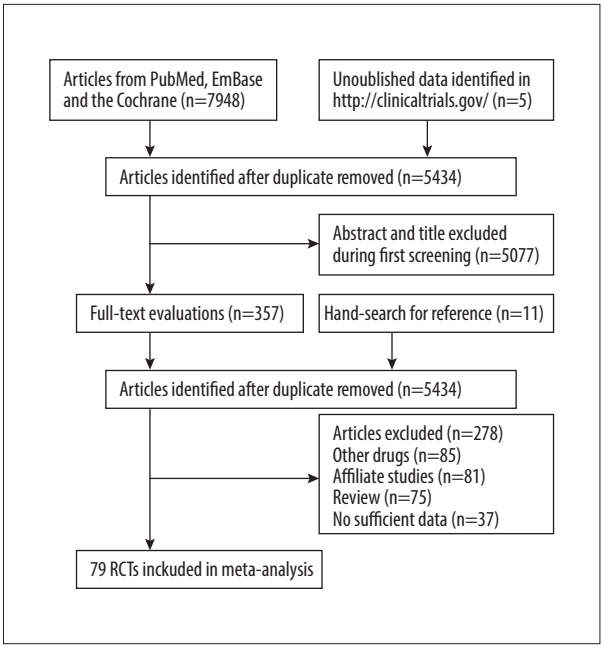

Figure 1. PRISMA flowchart for the literature search and study selection.

using odds ratios for dichotomous outcomes and standardized mean differences for continuous outcomes. For indirect and mixed comparisons, we used Bayesian network meta-analysis to compare different drugs [14]. To check for the presence of inconsistency, we used the loop-specific approach to assess the difference between direct and indirect estimates for a specific comparison in the loop [15]. To check the assumption of consistency in the entire network, we used the design-by-treatment interaction inconsistency model [14]. Because of the heterogeneity in patients, we still used the inconsistent model to analyze data. To rank the treatments for each outcome, we used surface under the cumulative ranking (SUCRA) probabilities [16]. Comparison-adjusted funnel plots were used to determine whether small-study effects were present in our analysis [17]. The summary results for adverse events for each drug were calculated using the random-effects model [13,18], and heterogeneity was assessed using I^2 and Q statistics [19,20]. All tests were two-tailed, and a *P* value of <0.05 was considered statistically significant. Data analyses were performed using Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Literature Search

The results of the study selection process are shown in **Figure 1**. The initial electronic searches provided 5434 articles after removal of duplicates. After reviewing the titles and abstracts, 5077 of these articles were excluded owing to irrelevant topics. The remaining 357 articles were retrieved for full-text evaluations, and 278 were excluded for the following reasons: other drugs (n=85), affiliate studies (n=81), review (n=75), and insufficient data (n=37). A manual search of the reference lists of these studies did not yield any new eligible studies. Finally, 79 RCTs that assessed a total of 108 797 patients were included in our systematic review. The baseline characteristics of these studies are summarized in the **Supplementary Material**.

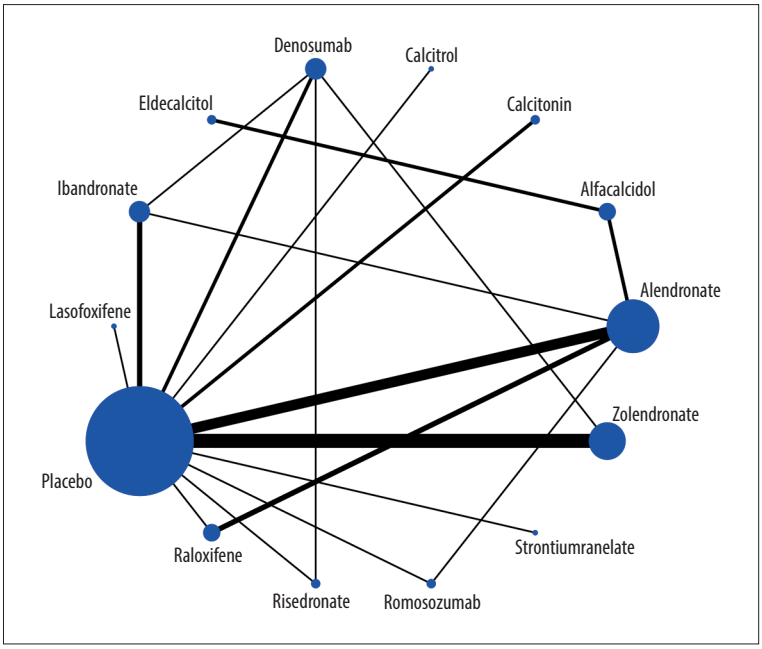

Figure 2. Network of comparisons for all fracture included in the analysis, Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

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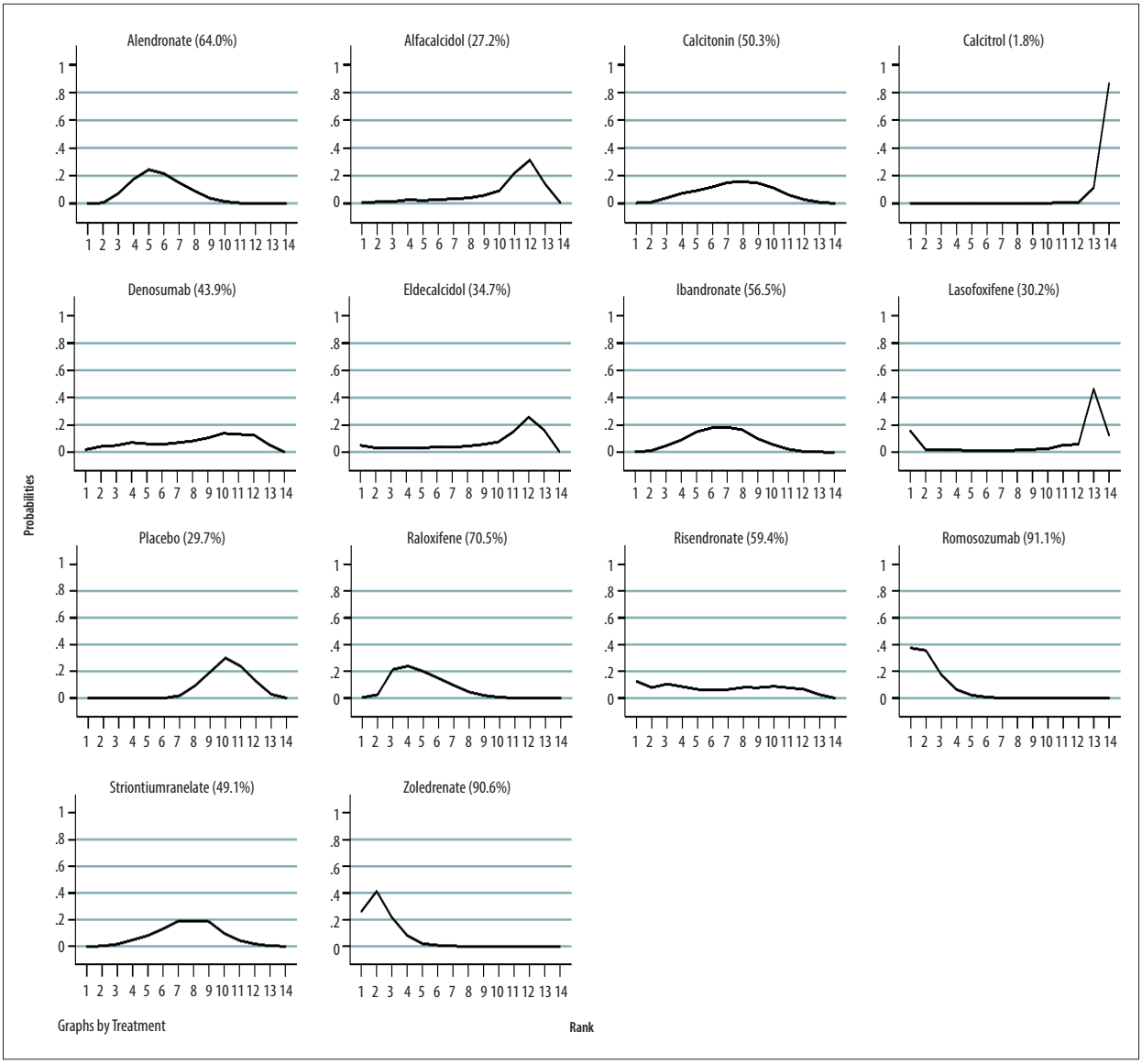

Figure 3. The SUCRA rank test for all fracture, Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

Study Characteristics

These studies were published from 1984 to 2020, with 39 to 9331 patients included in each trial, and the follow-up period was 0.5-5.0 years. Eleven RCTs included men only, 56 RCTs included women only, and the remaining 12 RCTs included both males and females. Sixty-nine trials reported patients using calcium supplementation, and 57 trials reported patients using vitamin D supplementation in intervention and control groups. Study quality was evaluated using the Jadad scale, in which 36 trials scored 4, 30 trials scored 3, 9 trials scored 2, and the remaining 4 trials scored 1.

Primary Endpoints

In the network meta-analysis, eligible comparisons of outcomes are presented in the network plot (**Figure 2**). In the figure, the nodes are weighted according to the number of studies that evaluated each treatment, and the edges were weighted according to the precision of the direct estimate for each pairwise comparison. An inconsistency plot was produced to assume the loop-specific heterogeneity estimate, exp (IF), which showed no significant differences among the studies. We ranked the comparative effects of the drugs with SUCRA probabilities (%). The results indicated that romosozumab (92.1%) and zoledronate (90.6%) were more effective in preventing all fracture risks (**Figure 3**). The details of the pairwise comparisons agents are presented in **Figure 4** and

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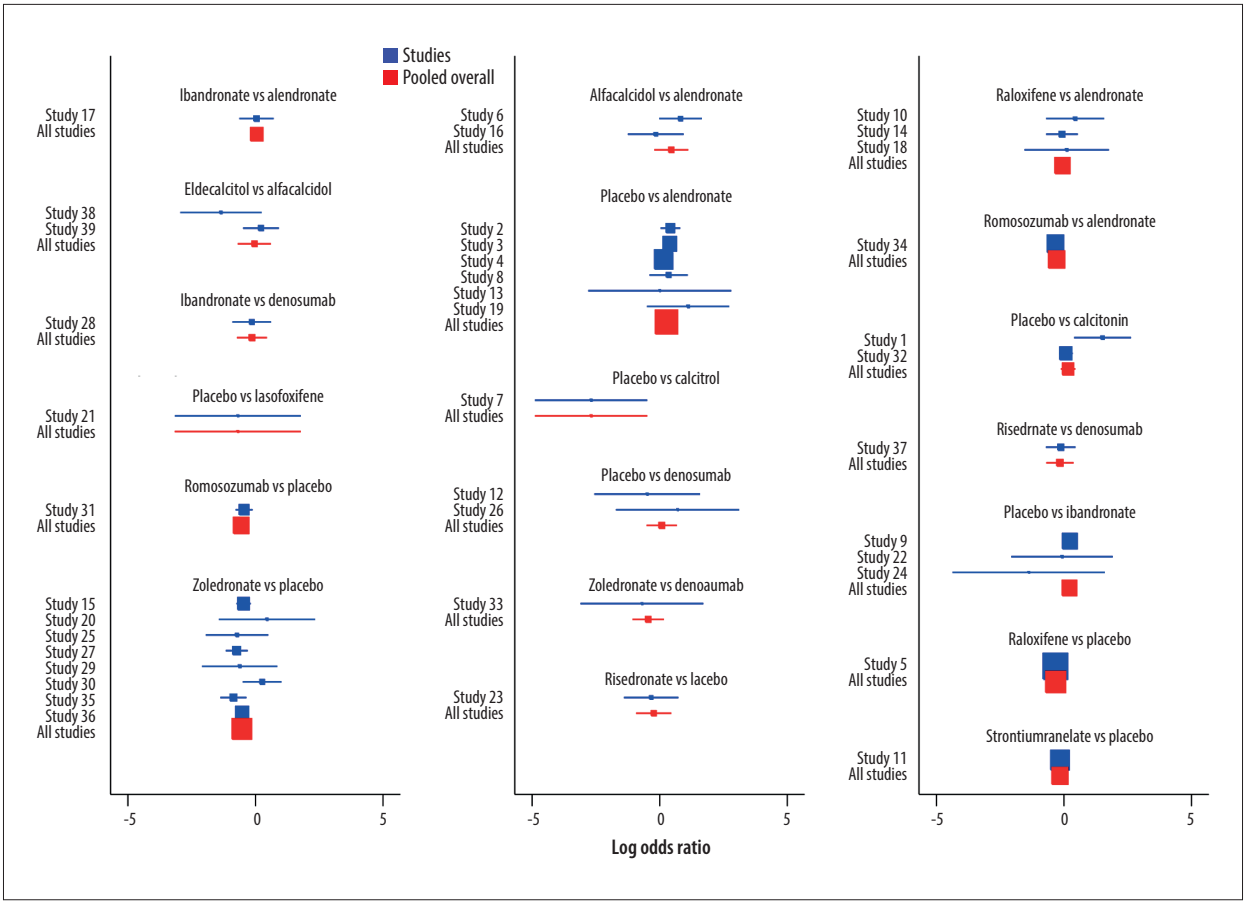

Figure 4. The pairwise comparisons agents for all fracture, Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

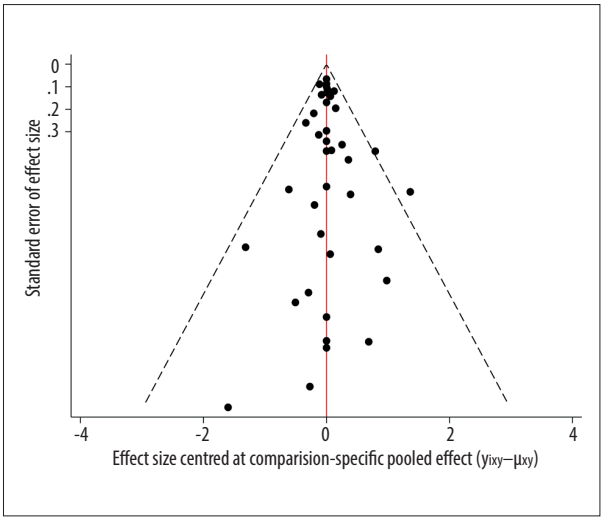

Figure 5. Funnel plot for all fracture, Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

the **Supplementary Material**. A comparison-adjusted funnel plot used to assess publication bias and determine the presence of small-study effects did not suggest that there was any publication bias (**Figure 5**).

The network meta-analysis comparing the effectiveness of various drugs to reduce the risk of vertebral and non-vertebral fracture is presented in **Figure 6**. The loop-specific heterogeneity inconsistency plot showed no significant differences. The SUCRA rank showed that abaloparatide (97.2%), denosumab (85.5%), and romosozumab (91.2%) were more effective for reducing the risk of vertebral fractures (**Figure 7A**), while abaloparatide (88.0%), and zoledronate (85.0%) were most likely to prevent the risk of non-vertebral fractures (**Figure 7B**). The details of the pairwise comparisons agents for the risk of vertebral and non-vertebral fractures are shown in **Figure 8** and **Supplementary Material**. There was no significant publication bias for the risk of vertebral and non-vertebral fracture (**Figure 9**).

Secondary Endpoints

The results of the network meta-analysis comparing the effectiveness of various drugs to reduce the risk of hip fracture and

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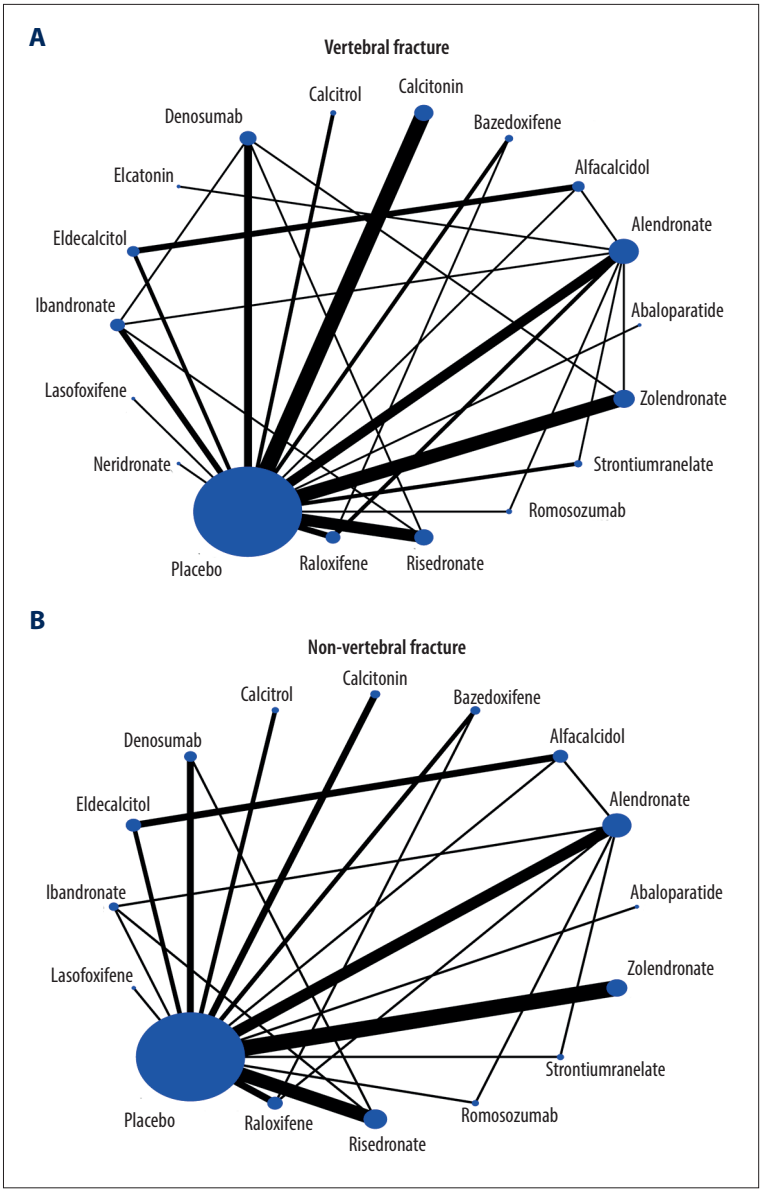

Figure 6. Network of comparisons for vertebral fracture (**A**) and non-vertebral fracture (**B**) included in the analysis, Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

peripheral fracture are shown in the **Supplementary Material**. We noted the best treatment agent for hip fracture was romosozumab (92.5%), while alendronate (61.0%), calcitonin (64.9%), and zoledronate (64.7%) provided similar effects on the risk of peripheral fracture. The pairwise comparisons agents supported the results for hip fracture, while no significant differences were obtained for the risk of peripheral fracture (**Supplementary Material**).

The network meta-analysis showing the effects of various drugs on BMD at various sites are shown in the **Supplementary Material**. The results of the SUCRA rank tests indicated that alendronate (100.0%), strontium ranelate (95.7%), ibandronate (92.4%), risedronate (86.7%), and ibandronate (95.5%) provided better effects for improving whole-body BMD, spine BMD, hip BMD, femoral neck BMD, and trochanter BMD, respectively (**Supplementary Material**). The results of pairwise comparisons agents for BMD at various sites were consistent with the SUCRA rank (**Supplementary Material**). We did not find significant publication bias for whole-body BMD, while potential significant publication bias for spine BMD, hip BMD, femoral neck BMD, and trochanter BMD was observed (**Supplementary Material**).

The safety profiles for each drug were also pooled and listed in the **Supplementary Material**. The use of bazedoxifene was associated with the highest incidence of any upper-gastrointestinal event (incidence: 0.48; 95% CI: 0.42-0.54), nasopharyngitis (incidence: 0.57; 95% CI: 0.51-0.63), headache (incidence: 0.10; 95% CI: 0.07-0.14), and back pain (incidence: 0.18;

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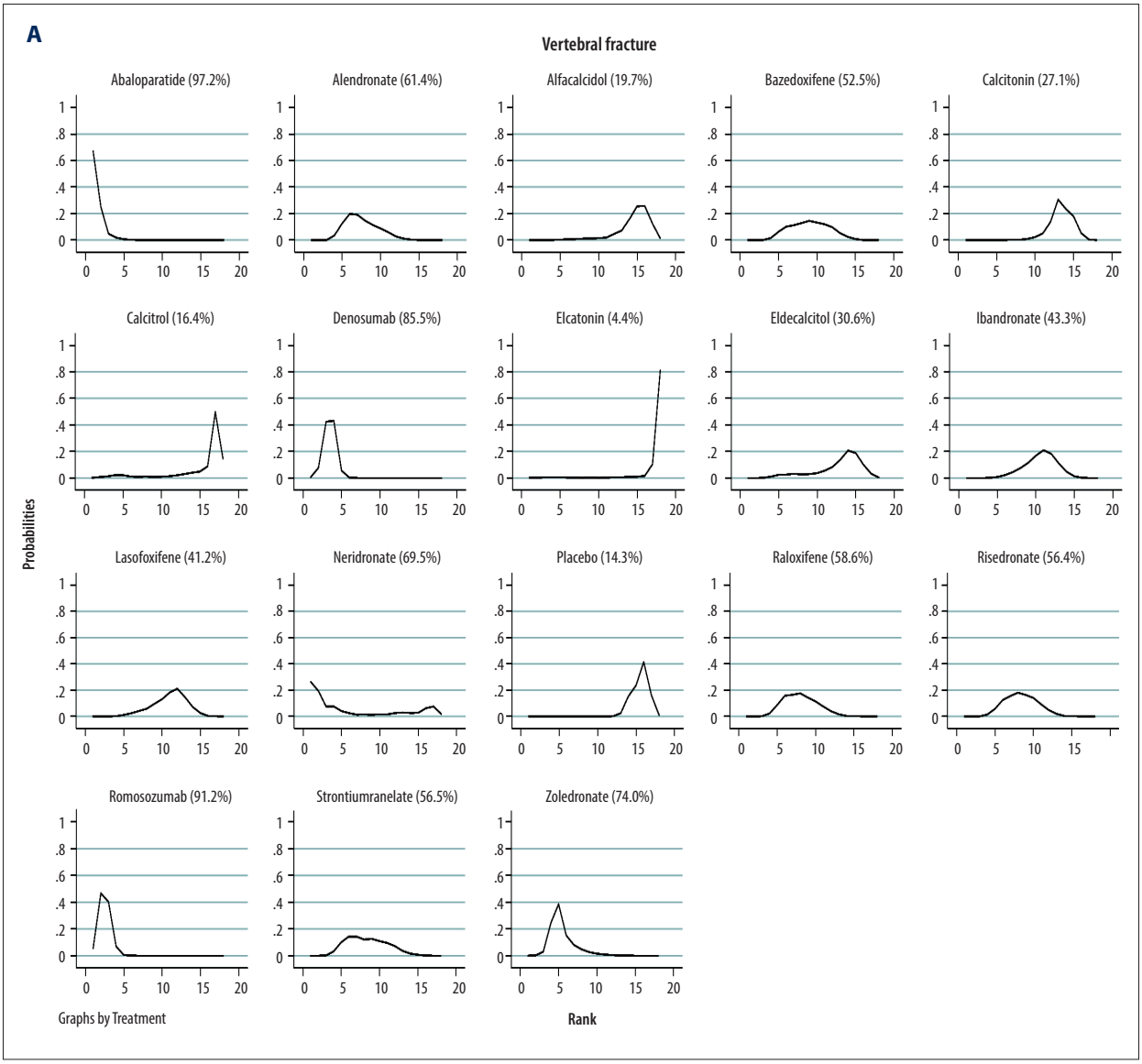
95% CI: 0.13-0.22). The highest incidence of musculoskeletal pain was observed with denosumab (incidence: 0.13; 95% CI: 0.10-0.17). The use of calcitonin was associated with the highest incidence of nausea (incidence: 0.15; 95% CI: 0.14-0.17).

Discussion

In this study, we performed a network meta-analysis to compare the effectiveness of various pharmacological therapies for osteoporotic patients. This large quantitative study included 108 797 individuals from 79 RCTs with a broad range of baseline characteristics. This meta-analysis indicated that romosozumab and zoledronate yielded better pharmacological outcomes for all fractures. Abaloparatide, denosumab, and romosozumab were found to be effective for preventing vertebral fractures. Abaloparatide and zoledronate were the most effective for preventing non-vertebral fractures. Romosozumab was the most effective for preventing hip fracture, while alendronate (61.0%), calcitonin (64.9%), and zoledronate provided similar reduction of the risk of peripheral fracture. Furthermore, the best therapeutic effects for improving whole-body BMD, spine BMD, hip BMD, femoral neck BMD, and trochanter BMD were alendronate, strontium ranelate, ibandronate, risedronate, and ibandronate, respectively. Finally, several adverse events should be addressed in clinical practice, including bazedoxifene-related to upper-gastrointestinal events, nasopharyngitis, headache, and back pain, denosumab related to musculoskeletal pain, and calcitonin related to nausea.

Several systematic reviews and meta-analyses have previously compared various pharmacological therapies for osteoporosis



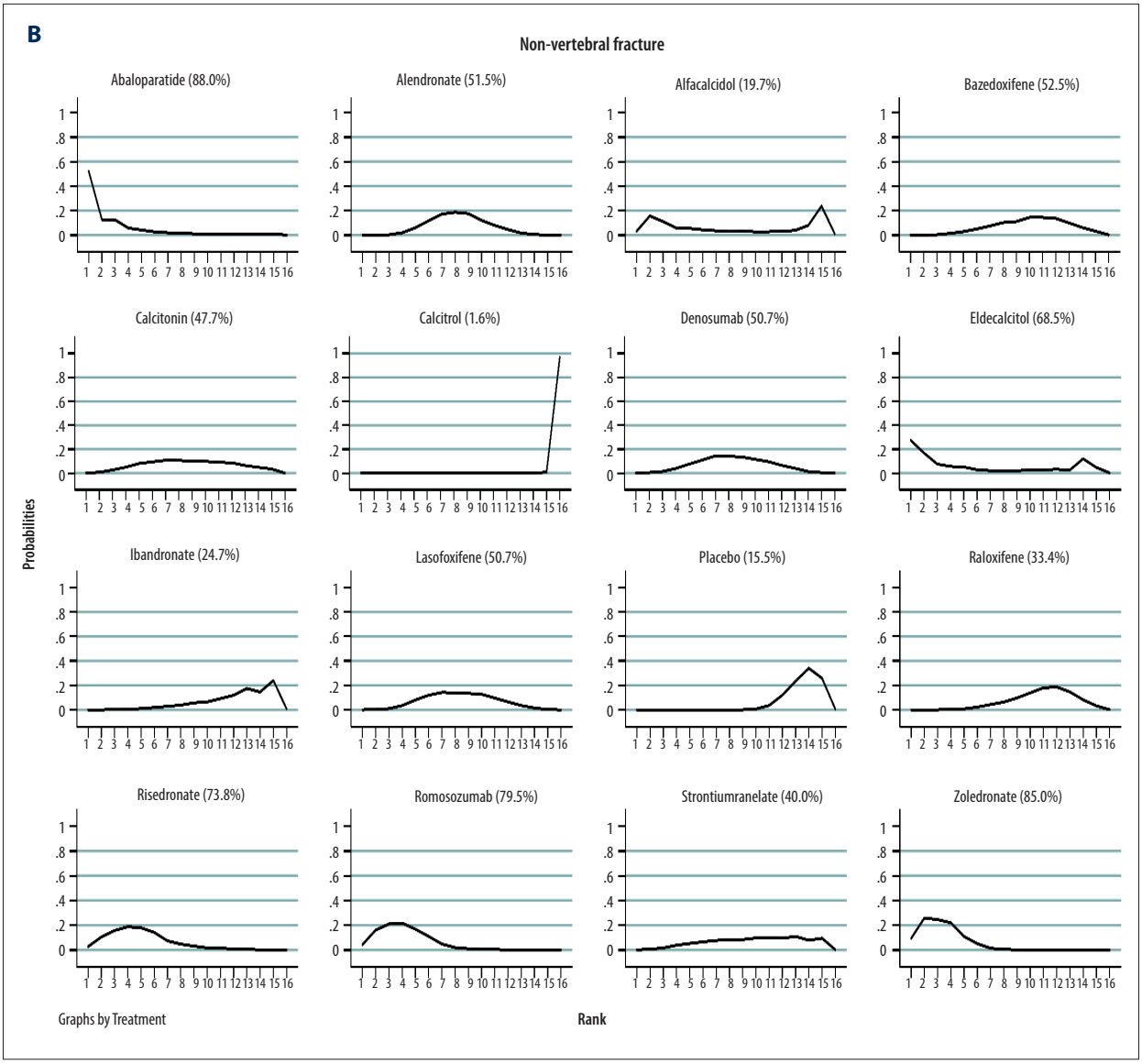


Figure 7. The SUCRA rank test for vertebral fracture (**A**) and non-vertebral fracture (**B**), Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

[7-9]. Moreover, a recent network meta-analysis conducted by Kataoka et al to compare the recommendation pharmacological therapies for postmenopausal osteoporosis and found no apparent discrepancy between guideline recommendations and drug prescribing rankings [21]. Deng et al identified 56 RCTs and found that bisphosphonates, teriparatide, and denosumab were associated with a reduced risk of fracture in patients undergoing glucocorticoids, while the anti-fracture efficacy of vitamin D metabolites and analogs were superior to plain vitamin D [22]. A network meta-analysis performed by Liu et al found teriparatide and ibandronate had the best effect in reducing vertebral and non-vertebral fractures in patients with glucocorticoid-induced osteoporosis [23]. Lin et al identified 94 RCTs and indicated that parathyroid hormone had the best effect in reducing hip fractures, while strontium ranelate, fluoride, and hormone replacement therapy provided the best efficacy in increasing BMD at total hip, lumbar spine, and distal radius [24]. Migliorini et al identified 64 RCTs and found denosumab had the best effect in increasing BMD at spine, hip, and femur in selected women with postmenopausal osteoporosis [25]. However, these studies focused on fractures at vertebral, non-vertebral, or hip, and BMD at various sites, while several other important outcomes, including all fractures, peripheral fractures, and safety profiles, were not addressed. Moreover, the analyses in prior meta-analyses contained several abandoned drugs, and the results might be overestimates based on network analysis. Furthermore, recently published RCTs should be entered into meta-analysis, and the pooled

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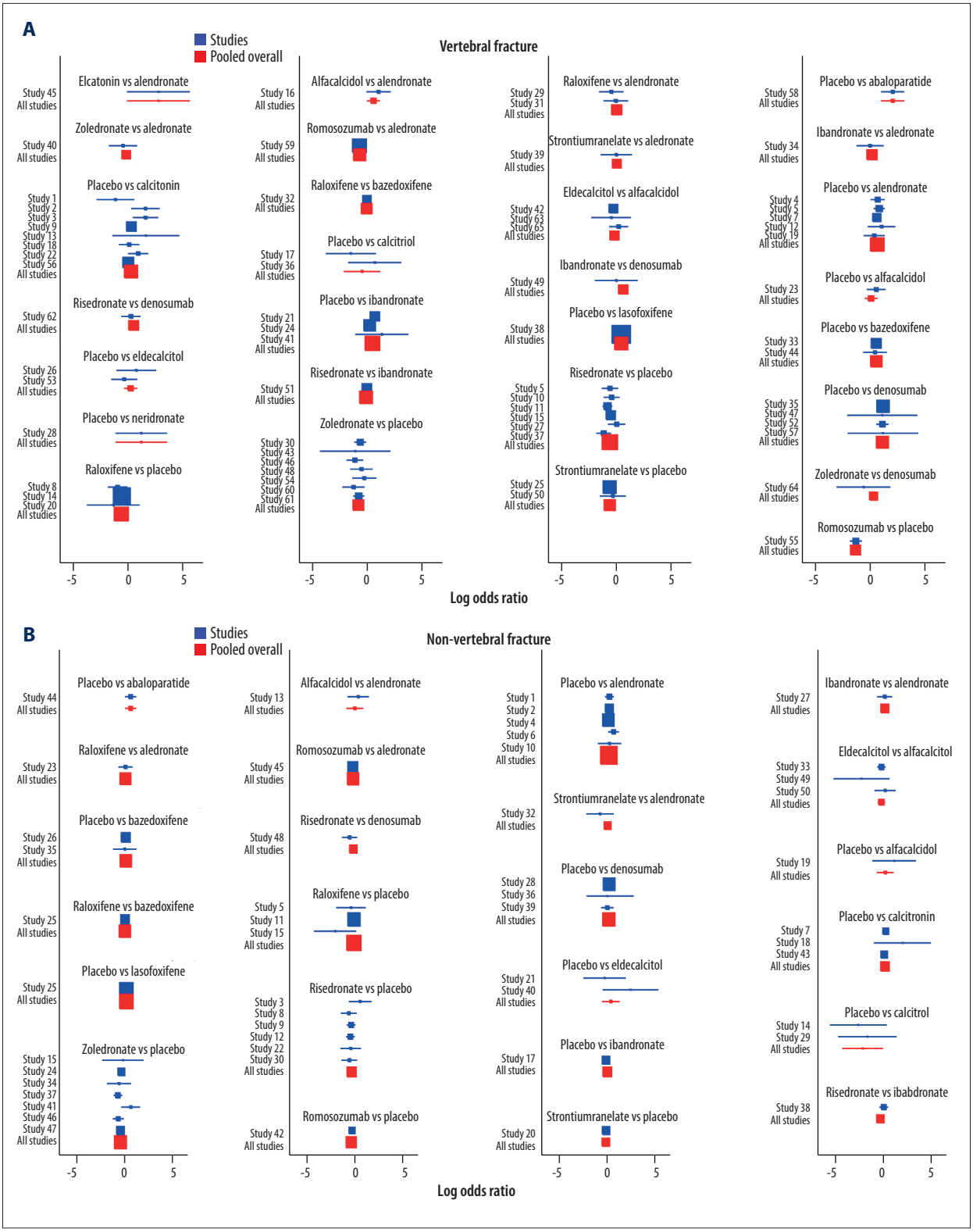

Figure 8. The pairwise comparisons agents for vertebral fracture (**A**) and non-vertebral fracture (**B**), Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

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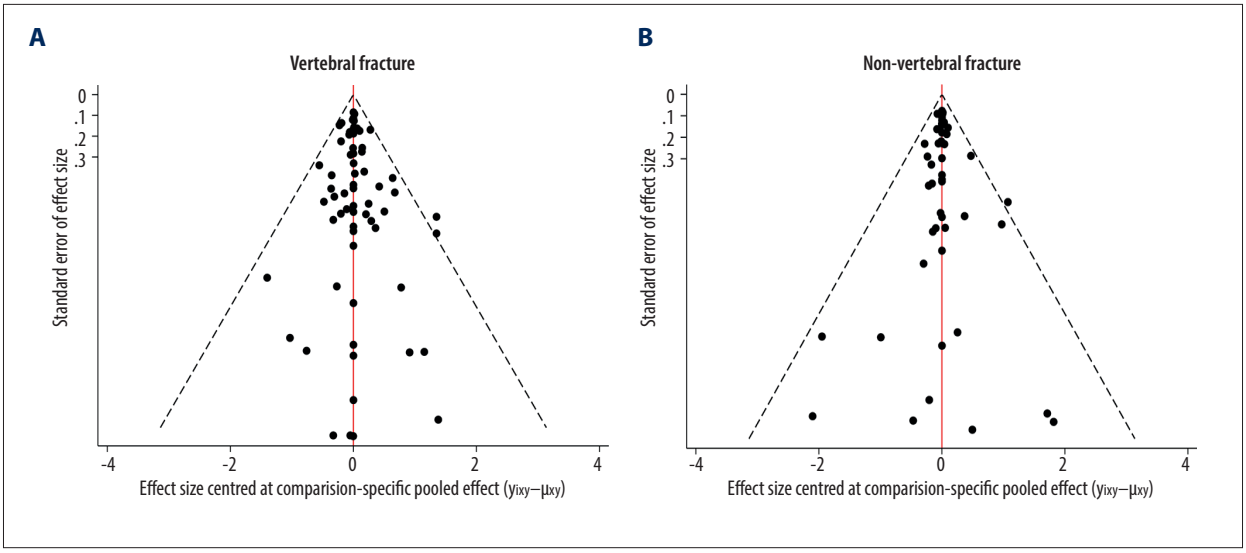

Figure 9. Funnel plots for vertebral fracture (**A**) and non-vertebral fracture (**B**), Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

conclusions require re-evaluation. Therefore, we performed a Bayesian network meta-analysis to provide evidence regarding better pharmacological therapies for osteoporosis treatment.

The study results indicated that romosozumab and zoledronate provided enhanced effectiveness for preventing all fractures. Several factors might explain these results: romosozumab provides a dual effect on bones owing to the changes in bone formation and bone resorption through binding and inhibiting sclerostin [26-30]; and the beneficial effects of zoledronate could be explained by the high potency of bisphosphonates and high compliance rate of patients [31]. Additionally, the relatively better agents for preventing vertebral and non-vertebral fractures were abaloparatide, denosumab, or romosozumab; and abaloparatide and zoledronate, respectively. Abaloparatide selectively binds to the RG versus R0 conformation of the parathyroid hormone type 1 receptor [32-37], subsequently affecting BMD, restoration of bone microarchitecture, and increased bone strength [38-40].

Our study also suggests the best agents for improving whole-body BMD, spine BMD, hip BMD, femoral neck BMD, and trochanter BMD were alendronate, strontium ranelate, ibandronate, risedronate, and ibandronate, respectively, which had already been illustrated in numerous studies [41-49]. Although our study found several other agents that more effectively improved BMD at various sites, these results might not be stable due to the smaller number of trials reporting these data. Further large-scale RCTs are required to verify these data. Finally, although numerous traditional systematic reviews and meta-analyses have already illustrated the effectiveness of pharmacological treatment for osteoporotic patients, direct or indirect comparisons among various agents remain inconclusive. The present comprehensive network meta-analysis studied various medicinal treatments for osteoporotic patients to further clarify the effectiveness of pharmacological therapies for osteoporosis. In addition, our study calculated the pooled incidences for adverse events related to each drug. However, Bayesian network meta-analysis was not conducted for specific adverse events because they were relatively uncommon.

Several limitations in our study should be acknowledged: (1) the use of vitamin D and calcium supplements by patients may have introduced heterogeneity across included trials; (2) the inconsistent results regarding the Bayesian network meta-analyses and pairwise comparisons should be verified by further direct comparison RCT; (3) nearly half of included studies had low to moderate quality, and the outcomes of this study should be interpreted cautiously; (4) although no significant publication bias was observed, the potential publication bias was inevitable owing to the analysis of our study based on published articles; and (5) there are inherent limitations for meta-analyses based on study level, and more detailed analyses are needed.

Conclusions

This network meta-analysis presents the optimal pharmacological therapies for preventing fracture, improving BMD at various sites, and potential adverse events in osteoporosis patients. These findings could be recommended in clinical practice for individuals at high risk of fractures. Further comprehensive network meta-analyses should be conducted to compare the cost-effectiveness of pharmacological therapies for osteoporosis.

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Declaration of Figures' Authenticity

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Supplementary Material

1. Search strategy

No	Terms
1	exp osteoporosis/ or osteopenia/ or osteoporo*.mp. or osteopeni*.mp. or osteopaen*.mp. or fragil*.mp.
2	exp bone density conservation agents/ or exp calcium/ or exp selective estrogen receptor modulators/ or exp vitamin d/
3	alendronate.mp. or ibandronate/ or residronate.mp. or zolendronate.mp. or bisphosphonate.mp. or disphosphonate.mp. or calcitonin.mp.
4	(raloxifen* or tamoxifen* or abaloparatide or romosozumab or bazedoxifene or lasofoxifene or denosumab or pth).mp.
5	randomized controlled trial.pt.
6	controlled clinical trial.pt.
7	randomized controlled trials/
8	random allocation.sh.
9	double blind method.sh.
10	single-blind method.sh.
11	clinical trial$.pt.
12	exp clinical trials/
13	(clinic$ adj25 trial$1).ti,ab.
14	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
15	placebos.sh. or placebo$.ti,ab.
16	random$.ti,ab.
17	research design.sh.
18	exp evaluation studies/
19	follow up studies.sh.
20	prospective studies.sh.
21	or/5-20
22	1 and (2 or 3 or 4)
23	21 and 22
24	limit 23 to (("human") and English)

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2. The baseline characteristics of included studies

Study	Country	Sample size	Mean age (years)	Sex	Intervention	Control	Calcium	Vitamin D	Follow-up (years)	Study quality
Gruber 1984 [s1]	USA	45 (24/21)	65.8/65.1	Women	Calcitonin	Placebo	Yes	Yes	2.0	1
Overgaard 1992 [s2]	Denmark	208 (156/52)	70.0/70.0	Women	Calcitonin	Placebo	Yes	No	2.0	4
Rico 1995 [s3]	Spain	72 (36/36)	68.8/69.6	Women	Calcitonin	Placebo	Yes	No	2.0	1
Liberman 1995 [s4]	Multicountries	878 (523/355)	64.0/64.0	Women	Alendronate	Placebo	Yes	No	3.0	4
Black 1996 [s5]	USA	2,027 (1,022/1,005)	70.7/71.0	Women	Alendronate	Placebo	Yes	Yes	3.0	4
Clemmesen 1997 [s6]	Multicountries	132 (88/44)	67.5/70.0	Women	Risedronate	Placebo	Yes	No	2.0	3
Cummings 1998 [s7]	USA	4,432 (2,214/2,218)	67.6/67.7	Women	Alendronate	Placebo	Yes	NA	4.2	4
Lufkin 1998 [s8]	USA	143 (95/48)	68.6/68.2	Women	Raloxifene	Placebo	Yes	Yes	1.0	3
Pols 1999 [s9]	Multicountries	1,908 (950/958)	62.8/62.8	Women	Alendronate	Placebo	Yes	No	1.0	2
Ettinger 1999 [s10]	Multicountries	6,828 (4,536/2,292)	66.0/66.3	Women	Raloxifene	Placebo	Yes	Yes	3.0	4
Harris 1999 [s11]	USA	2,458 (1,638/820)	69.0/68.0	Women	Risedronate	Placebo	Yes	Yes	3.0	4
Chesnut 2000 [s12]	Multicountries	1,255 (944/311)	68.4/68.2	Women	Calcitonin	Placebo	Yes	Yes	5.0	3
Fogelman 2000 [s13]	Multicountries	541 (361/180)	65.0/64.0	Women	Risedronate	Placebo	Yes	No	2.0	3
Reginster 2000 [s14]	Multicountries	1,226 (818/408)	71.0/71.0	Women	Risedronate	Placebo	Yes	Yes	3.0	4
Orwoll 2000 [s15]	Multicountries	244 (146/95)	63.0/63.0	Men	Alendronate	Placebo	Yes	Yes	2.0	4
Ushiroyama 2001 [s16]	Japan	151 (99/52)	53.9/51.0	Women	Calcitonin	Placebo	No	Yes	2.0	2
McClung 2001 [s17]	Multicountries	9,331 (6,197/3,134)	77.7/77.8	Women	Risedronate	Placebo	Yes	Yes	2.0	4
Ringe 2001 [s18]	Germany	134 (66/68)	53.3/52.7	Men	Alfacalcidol	Alendronate	Yes	No	2.0	3
Ebeling 2001 [s19]	Australia	39 (20/19)	57.5/60.5	Men	Calcitriol	Placebo	Yes	No	2.0	2
Dursun 2001 [s20]	Turkey	151 (101/50)	61.8/60.3	Women	Calcitriol	Alendronate	Yes	No	1.0	2
Greenspan 2002 [s21]	USA	327 (163/164)	78.5	Women	Alendronate	Placebo	Yes	Yes	2.0	4
Reid 2002 [s22]	Multicountries	351 (292/59)	64.0/57.0	Women	Zoledronate	Placebo	Yes	No	1.0	4
Morii 2003 [s23]	Japan	280 (183/97)	64.9/64.3	Women	Raloxifene	Placebo	Yes	Yes	1.0	4
Shiraki 2003 [s24]	Japan	166 (123/43)	60.5/60.5	Both	Risedronate	Placebo	Yes	No	0.8	3

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Study	Country	Sample size	Mean age (years)	Sex	Intervention	Control	Calcium	Vitamin D	Follow-up (years)	Study quality
Chesnut 2004 [s25]	Multicountries	2,929 (1,954/975)	69.0/69.0	Women	Ibandronate	Placebo	Yes	Yes	3.0	4
Ishida 2004 [s26]	Japan	198 (66/66/66)	69.0/71.0/ 68.0	Women	Calcitonin; alfacalcidol	Placebo	NA	No	2.0	3
Recker 2004 [s27]	Multicountries	2,860 (1,911/949)	67.0/67.0	Women	Ibandronate	Placebo	Yes	Yes	3.0	4
Luckey 2004 [s28]	USA	456 (223/233)	63.8/64.7	Women	Alendronate	Raloxifene	Yes	No	1.0	4
Meunier 2004 [s29]	Multicountries	1,442 (719/723)	69.4/69.2	Women	Strontium ranelate	Placebo	Yes	Yes	3.0	4
Matsumoto 2005 [s30]	Japan	219 (166/53)	67.0/68.0	Both	Eldecalcitol	Placebo	No	Yes	1.0	4
Hooper 2005 [s31]	Australia	383 (257/126)	52.7/52.6	Women	Risedronate	Placebo	Yes	No	2.0	3
Reginster 2005 [s32]	Multicountries	4,932 (2,479/2,453)	76.7/76.8	Women	Strontium ranelate	Placebo	Yes	Yes	3.0	4
Cascella 2005 [s33]	Italy	40 (20/20)	72.4/73.0	Women	Neridronate	Placebo	Yes	Yes	1.0	3
McClung 2006 [s34]	USA	365 (272/47/46)	62.1/62.8/63.7	Women	Denosumab; alendronate	Placebo	Yes	Yes	1.0	4
Recker 2007 [s35]	USA	1,423 (716/707)	65.7/65.5	Women	Alendronate	Raloxifene	Yes	Yes	0.9	3
Lyles 2007 [s36]	Multicountries	2,127 (1,065/1,062)	74.4/74.6	Both	Zoledronate	Placebo	Yes	Yes	1.9	4
Ringe 2007 [s37]	Germany	60 (30/30)	66.4/65.7	Both	Alfacalcidol	Alendronate	No	Yes	2.0	2
Iwamoto 2008 [s38]	Japan	122 (61/61)	70.3/68.5	Women	Alendronate	Raloxifene	Yes	No	1.0	1
Silverman 2008 [s39]	Multicountries	7,492 (3,758/1,849/1,885)	66.4/66.4/ 66.5	Women	Bazedoxifene; raloxifene	Placebo	Yes	Yes	3.0	3
Miller 2008 [s40]	Multicountries	1,733 (874/859)	65.6/65.6	Women	Ibandronate	Alendronate	Yes	Yes	1.0	3
Cosman 2009 [s41]	USA	99 (52/47)	67.8/68.3	Women	Alendronate	Raloxifene	Yes	Yes	1.5	2
Cummings 2009 [s42]	Multicountries	7,808 (3,902/3,906)	72.3/72.3	Women	Denosumab	Placebo	Yes	Yes	3.0	4
Yan 2009 [s43]	China	560 (280/280)	65.2/64.7	Women	Alendronate	Placebo	Yes	Yes	1.0	4
Grey 2009 [s44]	New Zealand	50 (25/25)	62.0/65.0	Women	Zoledronate	Placebo	No	No	2.0	3
Rogers 2009 [s45]	UK	51 (26/25)	63.4/63.6	Women	Lasofoxifene	Placebo	Yes	Yes	2.0	3
McClung 2009 [s46]	USA	160 (77/83)	53.7/53.4	Women	Ibandronate	Placebo	Yes	Yes	1.0	4
Xia 2009 [s47]	China	150 (74/76)	70.4/70.4	Women	Calcitriol	Placebo	Yes	Yes	1.0	3
Boonen 2009 [s48]	Multicountries	284 (191/93)	60.0/62.0	Men	Risedronate	Placebo	Yes	Yes	2.0	4
Ringe 2009 [s49]	Germany	316 (158/158)	55.8/58.0	Men	Risedronate	Placebo	Yes	Yes	2.0	1

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Study	Country	Sample size	Mean age (years)	Sex	Intervention	Control	Calcium	Vitamin D	Follow-up (years)	Study quality
Cummings 2010 [s50]	Multicountries	8,556 (5,704/2,852)	67.4/67.5	Women	Lasofoxifene	Placebo	Yes	Yes	5.0	4
Ringe 2010 [s51]	Germany	152 (76/76)	60.3/59.5	Men	Strontium ranelate	Alendronate	Yes	Yes	1.0	2
Orwoll 2010 [s52]	USA	302 (154/148)	64.5/63.5	Men	Zoledronate	Alendronate	Yes	Yes	2.0	3
Orwoll 2010 [s53]	USA	132 (85/47)	63.9/65.0	Men	Ibandronate	Placebo	Yes	Yes	1.0	3
Matsumoto 2011 [s54]	Japan	1,054 (528/526)	72.1/72.1	Both	Eldecalcitol	Alfacalcidol	NA	Yes	3.0	4
Cosman 2011 [s55]	Multicountries	275 (137/138)	65.0/63.8	Women	Zoledronate	Placebo	Yes	Yes	1.0	3
Itabashi 2011 [s56]	Japan	387 (259/128)	63.1/64.1	Women	Bazedoxifene	Placebo	Yes	Yes	2.2	3
Iwamoto 2011 [s57]	Japan	194 (97/97)	77.7/81.9	Women	Alendronate	Elcatonin	No	No	0.5	2
Boonen 2012 [s58]	Multicountries	1,199 (588/611)	66.0/66.0	Men	Zoledronate	Placebo	Yes	Yes	2.0	4
Orwoll 2012 [s59]	USA	242 (121/121)	64.9/65.0	Men	Denosumab	Placebo	Yes	Yes	1.0	3
Bai 2013 [s60]	China	483 (242/241)	56.5/57.2	Women	Zoledronate	Placebo	Yes	Yes	2.0	2
Recknor 2013 [s61]	Multicountries	833 (417/416)	67.2/66.2	Women	Denosumab	Ibandronate	Yes	Yes	1.0	3
Kaufman 2013 [s62]	Multicountries	261 (174/87)	73.1/72.6	Men	Strontium ranelate	Placebo	Yes	Yes	2.0	4
Nakamura 2013 [s63]	Japan	1,134 (758/376)	72.5/73.0	Both	Ibandronate	Risedronate	Yes	Yes	3.0	3
Grey 2014 [s64]	New Zealand	172 (129/43)	65.3/65.0	Women	Zoledronate	Placebo	No	No	2.0	3
Nakamura 2014 [s65]	Japan	952 (472/480)	69.9/69.0	Both	Denosumab	Placebo	Yes	Yes	2.0	3
Sakai 2015 [s66]	Japan	219 (110/109)	71.5/71.6	Both	Eldecalcitol	Placebo	Yes	No	1.0	3
Greenspan 2015 [s67]	USA	181 (89/92)	85.4/85.5	Women	Zoledronate	Placebo	Yes	Yes	2.0	4
Cosman 2016 [s68]	Multicountries	7,180 (3,589/3,591)	70.9/70.8	Women	Romosozumab	Placebo	Yes	Yes	1.0	4
Henriksen 2016 [s69]	Multicountries	4,665 (2,334/2,331)	66.5/67.0	Women	Calcitonin	Placebo	Yes	Yes	3.0	4
Koh 2016 [s70]	Korea	135 (69/66)	67.0/66.0	Women	Denosumab	Placebo	Yes	Yes	0.5	3
Miller 2016 [s71]	Multicountries	1,645 (824/821)	68.9/68.7	Women	Abaloparatide	Placebo	Yes	Yes	1.5	4
Miller 2016 [s72]	Multicountries	643 (321/322)	68.5/69.5	Women	Denosumab	Zoledronate	Yes	Yes	1.0	4
Saag 2017 [s73]	Multicountries	4,093 (2,046/2,047)	74.4/74.2	Women	Romosozumab	Alendronate	Yes	Yes	2.0	4
Nakamura 2017 [s74]	Japan	661 (330/331)	74.0/74.3	Both	Zoledronate	Placebo	Yes	Yes	2.0	3

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Study	Country	Sample size	Mean age (years)	Sex	Intervention	Control	Calcium	Vitamin D	Follow-up (years)	Study quality
Reid 2018 [s75]	New Zealand	2,000 (1,000/1,000)	71.0/71.0	Women	Zoledronate	Placebo	No	No	1.5	4
Saag 2019 [s76]	Multicountries	795 (398/397)	62.3/61.5	Both	Denosumab	Risedronate	Yes	Yes	2.0	4
Jiang 2019 [s77]	China	249 (128/121)	66.0/64.9	Both	Eldecalcitol	Alfacalcidol	No	No	1.0	3
Anastasilakis 2019 [s78]	Greece	57 (30/27)	64.8/65.2	Women	Denosumab	Zoledronate	Yes	Yes	2.0	3
Matsumoto 2020 [s79]	Japan	360 (178/182)	58.5/58.4	Both	Eldecalcitol	Alfacalcidol	Yes	No	2.0	3

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4. The therapeutic effects of pairwise comparisons agents on all fractures

Treatment/ comparator	Alendronate	Alfacalcidol	Calcitonin	Calcitriol	Denosumab	Eldecalcitol	Ibandronate	Lasofoxifene	Placebo	Raloxifene	Risedronate	Romosozumab	Strontiumranelate	Zoledronate
Alendronate	–	1.58 (0.81, 3.06)	1.11 (0.82, 1.51)	19.27 (2.12, 174.74)	1.21 (0.66, 2.22)	1.51 (0.60, 3.82)	1.05 (0.81, 1.36)	2.62 (0.22, 31.01)	1.31 (1.14, 1.51)	0.95 (0.77, 1.17)	1.03 (0.51, 2.08)	0.75 (0.62, 0.91)	1.12 (0.88, 1.43)	0.77 (0.62, 0.95)
Alfacalcidol	0.63 (0.33, 1.23)	–	0.71 (0.34, 1.47)	12.23 (1.22, 122.37)	0.77 (0.31, 1.89)	0.96 (0.50, 1.83)	0.67 (0.33, 1.37)	1.66 (0.13, 21.49)	0.83 (0.42, 1.64)	0.60 (0.30, 1.21)	0.66 (0.25, 1.72)	0.48 (0.24, 0.95)	0.71 (0.35, 1.44)	0.49 (0.24, 0.98)
Calcitonin	0.90 (0.66, 1.22)	1.42 (0.68, 2.94)	–	17.32 (1.88, 159.26)	1.09 (0.56, 2.10)	1.36 (0.51, 3.60)	0.95 (0.66, 1.36)	2.35 (0.20, 28.22)	1.18 (0.88, 1.57)	0.85 (0.61, 1.19)	0.93 (0.44, 1.96)	0.67 (0.47, 0.96)	1.00 (0.71, 1.42)	0.69 (0.50, 0.96)
Calcitriol	0.05 (0.01, 0.47)	0.08 (0.01, 0.82)	0.06 (0.01, 0.53)	–	0.06 (0.01, 0.61)	0.08 (0.01, 0.86)	0.05 (0.01, 0.50)	0.14 (0.00, 3.71)	0.07 (0.01, 0.61)	0.05 (0.01, 0.45)	0.05 (0.01, 0.54)	0.04 (0.00, 0.35)	0.06 (0.01, 0.53)	0.04 (0.00, 0.36)
Denosumab	0.83 (0.45, 1.52)	1.30 (0.53, 3.22)	0.92 (0.48, 1.78)	15.95 (1.63, 155.82)	–	1.25 (0.41, 3.80)	0.87 (0.48, 1.57)	2.17 (0.17, 27.44)	1.08 (0.60, 1.96)	0.78 (0.42, 1.45)	0.85 (0.50, 1.46)	0.62 (0.33, 1.16)	0.93 (0.49, 1.73)	0.64 (0.49, 1.73)
Eldecalcitol	0.66 (0.26, 1.68)	1.04 (0.55, 1.99)	0.74 (0.28, 1.96)	12.76 (1.17, 139.69)	0.80 (0.26, 2.43)	–	0.70 (0.27, 1.83)	1.73 (0.12, 24.32)	0.87 (0.34, 2.22)	0.63 (0.24, 1.63)	0.68 (0.21, 2.19)	0.50 (0.19, 1.28)	0.74 (0.28, 1.94)	0.51 (0.20, 1.32)
Ibandronate	0.95 (0.73, 1.23)	1.50 (0.73, 3.05)	1.06 (0.73, 1.52)	18.29 (2.00, 166.93)	1.15 (0.64, 2.06)	1.43 (0.55, 3.77)	–	2.48 (0.21, 29.60)	1.24 (1.00, 1.55)	0.90 (0.69, 1.18)	0.98 (0.49, 1.96)	0.71 (0.53, 0.96)	1.06 (0.79, 1.43)	0.73 (0.55, 0.96)
Lasofoxifene	0.38 (0.03, 4.53)	0.60 (0.05, 7.79)	0.43 (0.04, 5.10)	7.36 (0.27, 200.97)	0.46 (0.04, 5.85)	0.58 (0.04, 8.10)	0.40 (0.03, 4.80)	–	0.50 (0.04, 5.90)	0.36 (0.03, 4.29)	0.39 (0.03, 5.12)	0.29 (0.02, 3.41)	0.43 (0.04, 5.08)	0.29 (0.02, 3.49)
Placebo	0.76 (0.66, 0.88)	1.20 (0.61, 2.38)	0.85 (0.64, 1.13)	14.73 (1.63, 132.95)	0.92 (0.51, 1.67)	1.15 (0.45, 2.96)	0.81 (0.65, 1.00)	2.00 (0.17, 23.60)	–	0.72 (0.62, 0.85)	0.79 (0.40, 1.57)	0.57 (0.47, 0.70)	0.85 (0.70, 1.04)	0.59 (0.50, 0.69)
Raloxifene	1.06 (0.86, 1.30)	1.66 (0.83, 3.35)	1.18 (0.84, 1.64)	20.35 (2.24, 184.77)	1.28 (0.69, 2.36)	1.59 (0.61, 4.15)	1.11 (0.85, 1.46)	2.76 (0.23, 32.79)	1.38 (1.18, 1.62)	–	1.09 (0.54, 2.21)	0.79 (0.61, 1.02)	1.18 (0.92, 1.52)	0.81 (0.65, 1.02)
Risedronate	0.97 (0.48, 1.95)	1.53 (0.58, 4.02)	1.08 (0.51, 2.27)	18.66 (1.86, 187.15)	1.17 (0.69, 1.99)	1.46 (0.46, 4.69)	1.02 (0.51, 2.04)	2.53 (0.20, 32.87)	1.27 (0.64, 2.52)	0.92 (0.45, 1.86)	–	0.73 (0.35, 1.49)	1.08 (0.53, 2.22)	0.74 (0.37, 1.51)
Romosozumab	1.33 (1.10, 1.62)	2.10 (1.05, 4.21)	1.48 (1.04, 2.11)	25.72 (2.82, 234.43)	1.61 (0.86, 3.02)	2.02 (0.78, 5.21)	1.41 (1.04, 1.90)	3.49 (0.29, 41.58)	1.75 (1.42, 2.15)	1.26 (0.98, 1.64)	1.38 (0.67, 2.83)	–	1.49 (1.12, 1.99)	1.03 (0.79, 1.34)
Strontiumranelate	0.89 (0.70, 1.14)	1.41 (0.69, 2.87)	1.00 (0.70, 1.41)	17.24 (1.89, 157.05)	1.08 (0.58, 2.02)	1.35 (0.52, 3.54)	0.94 (0.70, 1.27)	2.34 (0.20, 27.86)	1.17 (0.96, 1.43)	0.85 (0.66, 1.09)	0.92 (0.45, 1.89)	0.67 (0.50, 0.89)	–	0.69 (0.53, 0.89)
Zoledronate	1.30 (0.53, 0.89)	2.05 (1.02, 4.13)	1.45 (1.04, 2.01)	25.06 (2.76, 227.63)	1.57 (0.85, 2.90)	1.96 (0.76, 5.10)	1.37 (1.04, 1.80)	3.40 (0.29, 40.39)	1.70 (1.45, 2.00)	1.23 (0.98, 1.55)	1.34 (0.66, 2.72)	0.97 (0.75, 1.27)	1.45 (1.12, 1.88)	–

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5. The therapeutic effects of pairwise comparisons agents on vertebral fractures

	Treatment								
Comparator	**Abaloparatide**	**Alendronate**	**Alfacalcidol**	**Bazedoxifene**	**Calcitonin**	**Calcitriol**	**Denosumab**	**Elcatonin**	**Eldecalcitol**
Abaloparatide		4.08	7.19	4.45	5.92	12.48	2.55	65.96	6.11
		(1.38, 12.07)	(2.15, 24.06)	(1.49, 13.30)	(2.00, 17.53)	(1.73, 90.15)	(0.86, 7.60)	(3.04, 1433.35)	(1.80, 20.78)
Alendronate	0.25		1.76	1.09	1.45	3.06	0.63	16.16	1.5
	(0.08, 0.72)		(0.97, 3.20)	(0.77, 1.55)	(1.05, 2.01)	(0.57, 16.48)	(0.45, 0.88)	(0.91, 288.33)	(0.79, 2.82)
Alfacalcidol	0.14	0.57		0.62	0.82	1.73	0.36	9.17	0.85
	(0.04, 0.47)	(0.31, 1.03)		(0.33, 1.17)	(0.44, 1.53)	(0.30, 10.15)	(0.19, 0.67)	(0.48, 173.98)	(0.61, 1.19)
Bazedoxifene	0.22	0.92	1.62		1.33	2.8	0.57	14.82	1.37
	(0.08, 0.67)	(0.65, 1.30)	(0.85, 3.06)		(0.93, 1.89)	(0.52, 15.21)	(0.39, 0.83)	(0.81, 269.96)	(0.70, 2.68)
Calcitonin	0.17	0.69	1.22	0.75		2.11	0.43	11.15	1.03
	(0.06, 0.50)	(0.50, 0.96)	(0.65, 2.27)	(0.53, 1.07)		(0.39, 11.38)	(0.30, 0.62)	(0.61, 202.55)	(0.53, 2.00)
Calcitriol	0.08	0.33	0.58	0.36	0.47		0.2	5.29	0.49
	(0.01, 0.58)	(0.06, 1.76)	(0.10, 3.37)	(0.07, 1.94)	(0.09, 2.56)		(0.04, 1.11)	(0.19, 148.86)	(0.08, 2.90)
Denosumab	0.39	1.6	2.82	1.74	2.32	4.89		25.83	2.39
	(0.13, 1.17)	(1.14, 2.25)	(1.50, 5.29)	(1.20, 2.53)	(1.62, 3.31)	(0.90, 26.44)		(1.42, 470.19)	(1.24, 4.63)
Elcatonin	0.02	0.06	0.11	0.07	0.09	0.19	0.04		0.09
	(0.00, 0.33)	(0.00, 1.10)	(0.01, 2.07)	(0.00, 1.23)	(0.00, 1.63)	(0.01, 5.33)	(0.00, 0.70)		(0.00, 1.77)
Eldecalcitol	0.16	0.67	1.18	0.73	0.97	2.04	0.42	10.8	
	(0.05, 0.56)	(0.35, 1.26)	(0.84, 1.65)	(0.37, 1.42)	(0.50, 1.88)	(0.35, 12.09)	(0.22, 0.81)	(0.56, 206.39)	
Ibandronate	0.21	0.85	1.49	0.92	1.23	2.59	0.53	13.69	1.27
	(0.07, 0.61)	(0.63, 1.15)	(0.81, 2.76)	(0.66, 1.30)	(0.91, 1.66)	(0.48, 13.93)	(0.38, 0.74)	(0.76, 248.20)	(0.66, 2.43)
Lasofoxifene	0.2	0.82	1.45	0.9	1.2	2.52	0.52	13.33	1.23
	(0.07, 0.60)	(0.60, 1.14)	(0.78, 2.71)	(0.63, 1.29)	(0.86, 1.67)	(0.47, 13.60)	(0.37, 0.73)	(0.73, 242.22)	(0.64, 2.38)
Neridronate	0.43	1.76	3.1	1.92	2.55	5.38	1.1	28.44	2.63
	(0.03, 5.74)	(0.16, 18.87)	(0.27, 35.27)	(0.18, 20.68)	(0.24, 27.39)	(0.30, 97.00)	(0.10, 11.84)	(0.68, 1188.42)	(0.23, 30.21)
Placebo	0.13	0.52	0.93	0.57	0.76	1.6	0.33	8.48	0.79
	(0.04, 0.37)	(0.42, 0.66)	(0.52, 1.65)	(0.44, 0.75)	(0.60, 0.96)	(0.30, 8.52)	(0.25, 0.42)	(0.47, 152.71)	(0.43, 1.45)
Raloxifene	0.24	0.97	1.71	1.06	1.4	2.96	0.61	15.65	1.45
	(0.08, 0.70)	(0.72, 1.31)	(0.92, 3.16)	(0.79, 1.41)	(1.04, 1.90)	(0.55, 15.94)	(0.43, 0.85)	(0.86, 283.72)	(0.76, 2.78)
Risedronate	0.23	0.95	1.67	1.03	1.38	2.9	0.59	15.33	1.42
	(0.08, 0.68)	(0.70, 1.28)	(0.91, 3.08)	(0.74, 1.45)	(1.02, 1.86)	(0.54, 15.58)	(0.43, 0.81)	(0.85, 277.85)	(0.74, 2.71)
Romosozumab	0.5	2.02	3.56	2.2	2.93	6.18	1.26	32.66	3.03
	(0.16, 1.49)	(1.57, 2.60)	(1.88, 6.74)	(1.46, 3.32)	(1.98, 4.33)	(1.13, 33.75)	(0.85, 1.89)	(1.81, 589.28)	(1.55, 5.92)
Strontium-ranelate	0.23	0.96	1.69	1.04	1.39	2.93	0.6	15.46	1.43
	(0.08, 0.70)	(0.67, 1.36)	(0.89, 3.19)	(0.71, 1.54)	(0.96, 2.00)	(0.54, 15.88)	(0.41, 0.87)	(0.85, 281.85)	(0.73, 2.80)
Zoledronate	0.29	1.18	2.08	1.29	1.71	3.6	0.74	19.06	1.77
	(0.10, 0.87)	(0.82, 1.69)	(1.09, 3.96)	(0.87, 1.91)	(1.18, 2.48)	(0.66, 19.62)	(0.50, 1.08)	(1.04, 347.75)	(0.90, 3.47)

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	Treatment								
Comparator	**Ibandronate**	**Lasofoxifene**	**Neridronate**	**Placebo**	**Raloxifene**	**Risedronate**	**Romosozumab**	**Strontium-ranelate**	**Zoledronate**
Abaloparatide	4.82	4.95	2.32	7.77	4.21	4.3	2.02	4.27	3.46
	(1.63, 14.20)	(1.67, 14.65)	(0.17, 30.87)	(2.69, 22.45)	(1.43, 12.44)	(1.46, 12.66)	(0.67, 6.10)	(1.43, 12.76)	(1.15, 10.39)
Alendronate	1.18	1.21	0.57	1.9	1.03	1.05	0.49	1.05	0.85
	(0.87, 1.60)	(0.88, 1.68)	(0.05, 6.09)	(1.52, 2.39)	(0.76, 1.40)	(0.78, 1.42)	(0.38, 0.64)	(0.74, 1.48)	(0.59, 1.22)
Alfacalcidol	0.67	0.69	0.32	1.08	0.59	0.6	0.28	0.59	0.48
	(0.36, 1.24)	(0.37, 1.28)	(0.03, 3.67)	(0.61, 1.93)	(0.32, 1.08)	(0.32, 1.10)	(0.15, 0.53)	(0.31, 1.12)	(0.25, 0.92)
Bazedoxifene	1.08	1.11	0.52	1.75	0.95	0.97	0.45	0.96	0.78
	(0.77, 1.52)	(0.78, 1.59)	(0.05, 5.61)	(1.33, 2.29)	(0.71, 1.26)	(0.69, 1.35)	(0.30, 0.68)	(0.65, 1.41)	(0.52, 1.15)
Calcitonin	0.81	0.84	0.39	1.31	0.71	0.73	0.34	0.72	0.58
	(0.60, 1.10)	(0.60, 1.16)	(0.04, 4.21)	(1.04, 1.66)	(0.53, 0.96)	(0.54, 0.98)	(0.23, 0.50)	(0.50, 1.04)	(0.40, 0.85)
Calcitriol	0.39	0.4	0.19	0.62	0.34	0.34	0.16	0.34	0.28
	(0.07, 2.08)	(0.07, 2.14)	(0.01, 3.35)	(0.12, 3.31)	(0.06, 1.82)	(0.06, 1.85)	(0.03, 0.88)	(0.06, 1.86)	(0.05, 1.51)
Denosumab	1.89	1.94	0.91	3.05	1.65	1.68	0.79	1.67	1.36
	(1.36, 2.63)	(1.37, 2.73)	(0.08, 9.76)	(2.36, 3.92)	(1.17, 2.32)	(1.23, 2.31)	(0.53, 1.18)	(1.15, 2.42)	(0.92, 1.99)
Elcatonin	0.07	0.08	0.04	0.12	0.06	0.07	0.03	0.06	0.05
	(0.00, 1.32)	(0.00, 1.36)	(0.00, 1.47)	(0.01, 2.12)	(0.00, 1.16)	(0.00, 1.18)	(0.00, 0.55)	(0.00, 1.18)	(0.00, 0.96)
Eldecalcitol	0.79	0.81	0.38	1.27	0.69	0.7	0.33	0.7	0.57
	(0.41, 1.51)	(0.42, 1.56)	(0.03, 4.35)	(0.69, 2.35)	(0.36, 1.32)	(0.37, 1.34)	(0.17, 0.65)	(0.36, 1.36)	(0.29, 1.11)
Ibandronate		1.03	0.48	1.61	0.87	0.89	0.42	0.89	0.72
		(0.75, 1.41)	(0.04, 5.15)	(1.31, 1.99)	(0.65, 1.17)	(0.70, 1.14)	(0.29, 0.61)	(0.62, 1.25)	(0.50, 1.03)
Lasofoxifene	0.97		0.47	1.57	0.85	0.87	0.41	0.86	0.7
	(0.71, 1.33)		(0.04, 5.03)	(1.24, 1.98)	(0.62, 1.17)	(0.64, 1.18)	(0.28, 0.60)	(0.60, 1.24)	(0.48, 1.01)
Neridronate	2.08	2.13		3.35	1.82	1.86	0.87	1.84	1.49
	(0.19, 22.24)	(0.20, 22.89)		(0.32, 35.56)	(0.17, 19.47)	(0.17, 19.85)	(0.08, 9.43)	(0.17, 19.82)	(0.14, 16.11)
Placebo	0.62	0.64	0.3		0.54	0.55	0.26	0.55	0.45
	(0.50, 0.76)	(0.50, 0.80)	(0.03, 3.16)		(0.44, 0.67)	(0.45, 0.68)	(0.19, 0.35)	(0.42, 0.72)	(0.33, 0.59)
Raloxifene	1.14	1.17	0.55	1.85		1.02	0.48	1.01	0.82
	(0.85, 1.53)	(0.85, 1.62)	(0.05, 5.90)	(1.48, 2.29)		(0.76, 1.36)	(0.33, 0.69)	(0.71, 1.44)	(0.57, 1.18)
Risedronate	1.12	1.15	0.54	1.81	0.98		0.47	0.99	0.8
	(0.88, 1.43)	(0.85, 1.56)	(0.05, 5.77)	(1.48, 2.21)	(0.73, 1.31)		(0.32, 0.68)	(0.70, 1.40)	(0.57, 1.14)
Romosozumab	2.39	2.45	1.15	3.85	2.09	2.13		2.11	1.71
	(1.65, 3.46)	(1.66, 3.61)	(0.11, 12.43)	(2.82, 5.25)	(1.44, 3.03)	(1.47, 3.08)		(1.40, 3.19)	(1.13, 2.61)
Strontium-ranelate	1.13	1.16	0.54	1.82	0.99	1.01	0.47		0.81
	(0.80, 1.60)	(0.81, 1.66)	(0.05, 5.86)	(1.38, 2.40)	(0.69, 1.41)	(0.72, 1.42)	(0.31, 0.71)		(0.54, 1.21)
Zoledronate	1.39	1.43	0.67	2.25	1.22	1.24	0.58	1.23	
	(0.98, 1.99)	(0.99, 2.07)	(0.06, 7.23)	(1.68, 3.00)	(0.85, 1.74)	(0.87, 1.77)	(0.38, 0.89)	(0.83, 1.84)	

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6. The therapeutic effects of pairwise comparisons agents on nonvertebral fractures

	Treatment									
Comparator	**Abaloparatide**	**Alendronate**	**Alfacalcidol**	**Bazedoxifene**	**Calcitonin**	**Calcitriol**	**Denosumab**	**Eldecalcitol**	**Ibandronate**	**Lasofoxifene**
Abaloparatide		1.55	1.54	1.65	1.57	16.26	1.55	1.26	1.81	1.55
		(0.85, 2.81)	(0.54, 4.43)	(0.90, 3.04)	(0.84, 2.95)	(1.79, 147.93)	(0.85, 2.84)	(0.42, 3.75)	(0.97, 3.39)	(0.85, 2.83)
Alendronate	0.65		0.99	1.07	1.02	10.5	1	0.81	1.17	1
	(0.36, 1.17)		(0.41, 2.39)	(0.86, 1.33)	(0.78, 1.33)	(1.24, 88.66)	(0.81, 1.23)	(0.32, 2.04)	(0.90, 1.51)	(0.82, 1.22)
Alfacalcidol	0.65	1.01		1.07	1.02	10.56	1.01	0.82	1.18	1.01
	(0.23, 1.87)	(0.42, 2.42)		(0.44, 2.64)	(0.41, 2.55)	(1.05, 105.83)	(0.41, 2.47)	(0.55, 1.21)	(0.47, 2.92)	(0.41, 2.46)
Bazedoxifene	0.6	0.94	0.93		0.95	9.83	0.94	0.76	1.1	0.94
	(0.33, 1.11)	(0.75, 1.16)	(0.38, 2.29)		(0.71, 1.28)	(1.16, 83.32)	(0.73, 1.20)	(0.30, 1.95)	(0.82, 1.47)	(0.74, 1.19)
Calcitonin	0.64	0.98	0.98	1.05		10.33	0.99	0.8	1.15	0.99
	(0.34, 1.19)	(0.75, 1.29)	(0.39, 2.44)	(0.78, 1.42)		(1.21, 88.05)	(0.74, 1.32)	(0.31, 2.07)	(0.82, 1.61)	(0.74, 1.31)
Calcitriol	0.06	0.1	0.09	0.1	0.1		0.1	0.08	0.11	0.1
	(0.01, 0.56)	(0.01, 0.80)	(0.01, 0.95)	(0.01, 0.86)	(0.01, 0.83)		(0.01, 0.81)	(0.01, 0.79)	(0.01, 0.95)	(0.01, 0.81)
Denosumab	0.64	1	0.99	1.07	1.02	10.48		0.81	1.17	1
	(0.35, 1.18)	(0.81, 1.23)	(0.41, 2.43)	(0.84, 1.36)	(0.76, 1.36)	(1.24, 88.77)		(0.32, 2.07)	(0.88, 1.55)	(0.80, 1.25)
Eldecalcitol	0.8	1.23	1.22	1.32	1.25	12.93	1.23		1.44	1.23
	(0.27, 2.37)	(0.49, 3.10)	(0.83, 1.81)	(0.51, 3.37)	(0.48, 3.25)	(1.27, 131.76)	(0.48, 3.15)		(0.56, 3.73)	(0.48, 3.15)
Ibandronate	0.55	0.85	0.85	0.91	0.87	8.98	0.86	0.69		0.86
	(0.29, 1.03)	(0.66, 1.11)	(0.34, 2.11)	(0.68, 1.22)	(0.62, 1.21)	(1.05, 76.48)	(0.64, 1.14)	(0.27, 1.80)		(0.65, 1.13)
Lasofoxifene	0.64	1	0.99	1.07	1.01	10.48	1	0.81	1.17	
	(0.35, 1.18)	(0.82, 1.21)	(0.41, 2.42)	(0.84, 1.35)	(0.76, 1.35)	(1.24, 88.59)	(0.80, 1.25)	(0.32, 2.06)	(0.88, 1.54)	
Placebo	0.53	0.83	0.82	0.88	0.84	8.67	0.83	0.67	0.97	0.83
	(0.30, 0.95)	(0.73, 0.93)	(0.34, 1.98)	(0.74, 1.05)	(0.66, 1.07)	(1.03, 72.95)	(0.70, 0.98)	(0.27, 1.69)	(0.77, 1.22)	(0.71, 0.96)
Raloxifene	0.59	0.91	0.91	0.97	0.93	9.58	0.91	0.74	1.07	0.91
	(0.32, 1.07)	(0.76, 1.10)	(0.37, 2.21)	(0.81, 1.17)	(0.70, 1.23)	(1.13, 80.99)	(0.73, 1.14)	(0.29, 1.89)	(0.81, 1.40)	(0.74, 1.13)
Risedronate	0.75	1.16	1.16	1.24	1.18	12.2	1.16	0.94	1.36	1.16
	(0.40, 1.40)	(0.90, 1.50)	(0.47, 2.87)	(0.93, 1.65)	(0.85, 1.64)	(1.43, 103.88)	(0.89, 1.53)	(0.36, 2.44)	(1.03, 1.80)	(0.89, 1.53)
Romosozumab	0.78	1.21	1.2	1.29	1.23	12.69	1.21	0.98	1.41	1.21
	(0.42, 1.44)	(1.01, 1.45)	(0.49, 2.94)	(0.99, 1.69)	(0.90, 1.68)	(1.49, 107.73)	(0.93, 1.57)	(0.38, 2.51)	(1.04, 1.91)	(0.94, 1.56)
Strontium-ranelate	0.61	0.94	0.93	1	0.95	9.84	0.94	0.76	1.1	0.94
	(0.32, 1.15)	(0.69, 1.26)	(0.37, 2.34)	(0.72, 1.39)	(0.66, 1.37)	(1.15, 84.25)	(0.68, 1.29)	(0.29, 1.99)	(0.76, 1.57)	(0.69, 1.29)
Zoledronate	0.82	1.27	1.27	1.36	1.3	13.39	1.28	1.03	1.49	1.28
	(0.45, 1.51)	(1.03, 1.57)	(0.52, 3.11)	(1.06, 1.74)	(0.97, 1.74)	(1.58, 113.36)	(1.01, 1.62)	(0.40, 2.65)	(1.12, 1.99)	(1.02, 1.60)

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	Treatment					
Comparator	**Placebo**	**Raloxifene**	**Risedronate**	**Romosozumab**	**Strontiumranelate**	**Zoledronate**
Abaloparatide	1.88	1.7	1.33	1.28	1.65	1.21
	(1.05, 3.36)	(0.93, 3.09)	(0.71, 2.49)	(0.69, 2.37)	(0.87, 3.15)	(0.66, 2.23)
Alendronate	1.21	1.1	0.86	0.83	1.07	0.78
	(1.07, 1.37)	(0.91, 1.32)	(0.67, 1.11)	(0.69, 0.99)	(0.79, 1.44)	(0.64, 0.97)
Alfacalcidol	1.22	1.1	0.87	0.83	1.07	0.79
	(0.50, 2.94)	(0.45, 2.69)	(0.35, 2.15)	(0.34, 2.04)	(0.43, 2.70)	(0.32, 1.94)
Bazedoxifene	1.13	1.03	0.81	0.78	1	0.73
	(0.95, 1.36)	(0.86, 1.23)	(0.60, 1.07)	(0.59, 1.01)	(0.72, 1.39)	(0.57, 0.94)
Calcitonin	1.19	1.08	0.85	0.81	1.05	0.77
	(0.94, 1.51)	(0.82, 1.43)	(0.61, 1.18)	(0.60, 1.11)	(0.73, 1.51)	(0.58, 1.03)
Calcitriol	0.12	0.1	0.08	0.08	0.1	0.07
	(0.01, 0.97)	(0.01, 0.88)	(0.01, 0.70)	(0.01, 0.67)	(0.01, 0.87)	(0.01, 0.63)
Denosumab	1.21	1.09	0.86	0.83	1.07	0.78
	(1.02, 1.43)	(0.88, 1.36)	(0.65, 1.13)	(0.64, 1.07)	(0.77, 1.47)	(0.62, 0.99)
Eldecalcitol	1.49	1.35	1.06	1.02	1.31	0.97
	(0.59, 3.75)	(0.53, 3.44)	(0.41, 2.74)	(0.40, 2.60)	(0.50, 3.44)	(0.38, 2.47)
Ibandronate	1.04	0.94	0.74	0.71	0.91	0.67
	(0.82, 1.31)	(0.71, 1.23)	(0.56, 0.97)	(0.52, 0.96)	(0.64, 1.31)	(0.50, 0.89)
Lasofoxifene	1.21	1.09	0.86	0.83	1.06	0.78
	(1.04, 1.41)	(0.89, 1.35)	(0.65, 1.13)	(0.64, 1.06)	(0.78, 1.46)	(0.62, 0.98)
Placebo		0.91	0.71	0.68	0.88	0.65
		(0.78, 1.05)	(0.57, 0.89)	(0.56, 0.84)	(0.67, 1.16)	(0.55, 0.77)
Raloxifene	1.1		0.79	0.76	0.97	0.72
	(0.96, 1.28)		(0.60, 1.03)	(0.59, 0.97)	(0.71, 1.33)	(0.57, 0.89)
Risedronate	1.41	1.27		0.96	1.24	0.91
	(1.12, 1.76)	(0.97, 1.66)		(0.71, 1.30)	(0.87, 1.77)	(0.69, 1.21)
Romosozumab	1.46	1.32	1.04		1.29	0.95
	(1.20, 1.79)	(1.04, 1.69)	(0.77, 1.40)		(0.92, 1.81)	(0.73, 1.23)
Strontium-ranelate	1.13	1.03	0.81	0.78		0.74
	(0.86, 1.49)	(0.75, 1.40)	(0.57, 1.15)	(0.55, 1.09)		(0.53, 1.02)
Zoledronate	1.54	1.4	1.1	1.06	1.36	
	(1.30, 1.83)	(1.12, 1.75)	(0.83, 1.45)	(0.81, 1.37)	(0.98, 1.88)	

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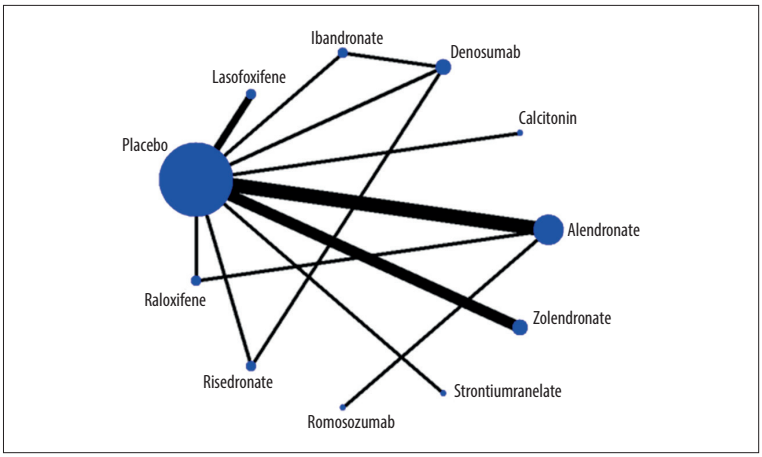
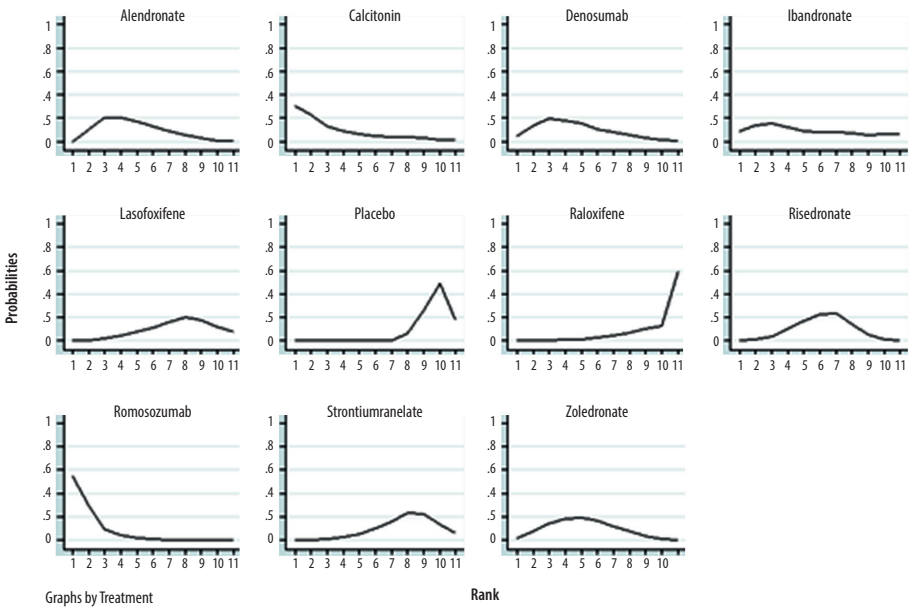
7. Hip fracture



Supplementary Figure 7-1. Network of comparisons for hip fractures included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
alendronate	62.8	0.1	4.7
calcitonin	77.2	30.1	3.3
denosumab	65.7	4.7	4.4
ibandronate	58.3	8.5	5.2
lasofoxifene	33.1	0.1	7.7
placebo	12.3	0.0	9.8
raloxifene	10.7	0.0	9.9
risedronate	48.0	0.1	6.2
romosozumab	92.5	54.8	1.7
strontiumranelate	30.0	0.0	8.0
zoledronate	59.4	1.6	5.1

Supplementary Figure 7-2. The SUCRA rank test for hip fracture.

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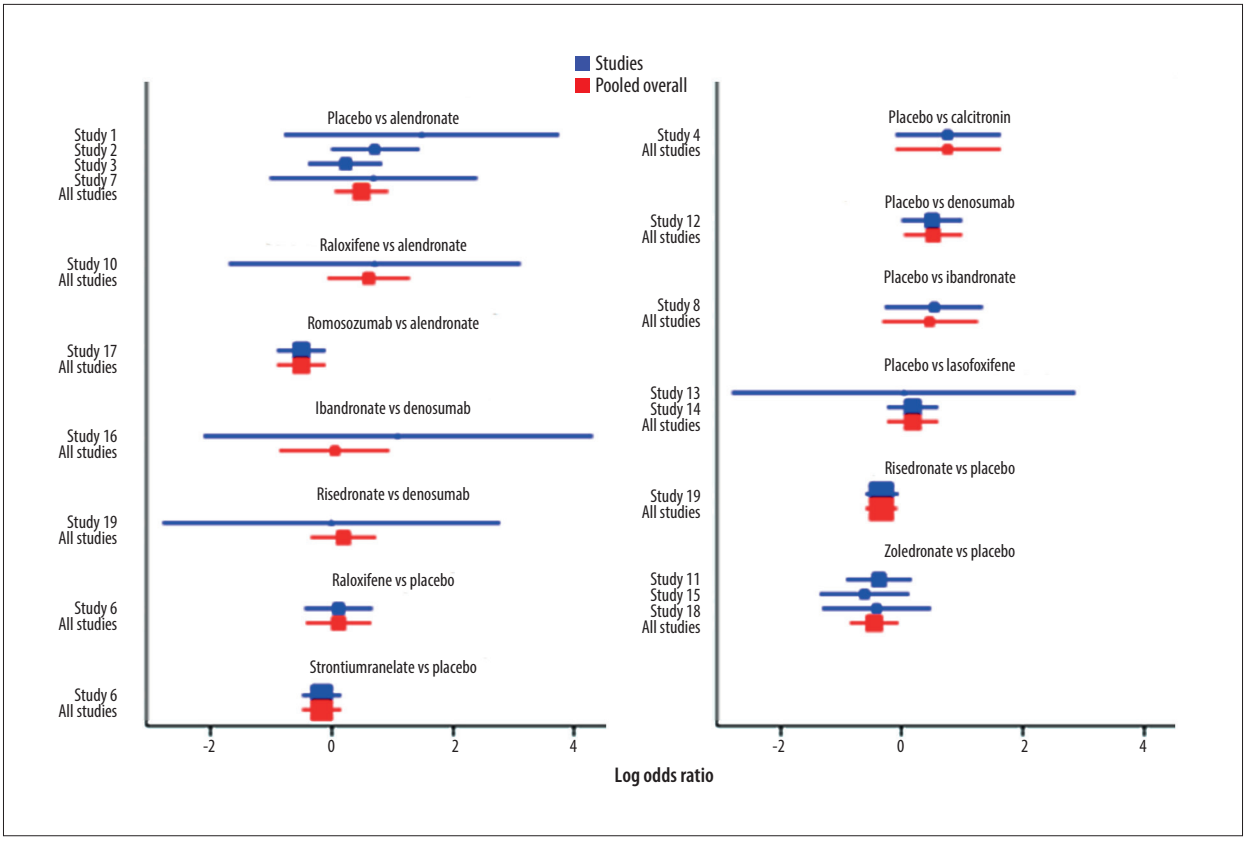
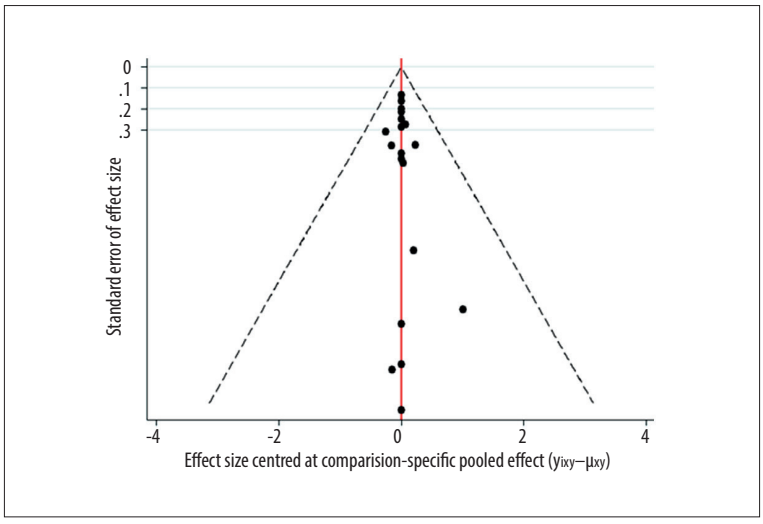


Supplementary Figure 7-3. The pairwise comparisons agents for hip fracture.



Supplementary Figure 7-4. Funnel plot for hip fracture.

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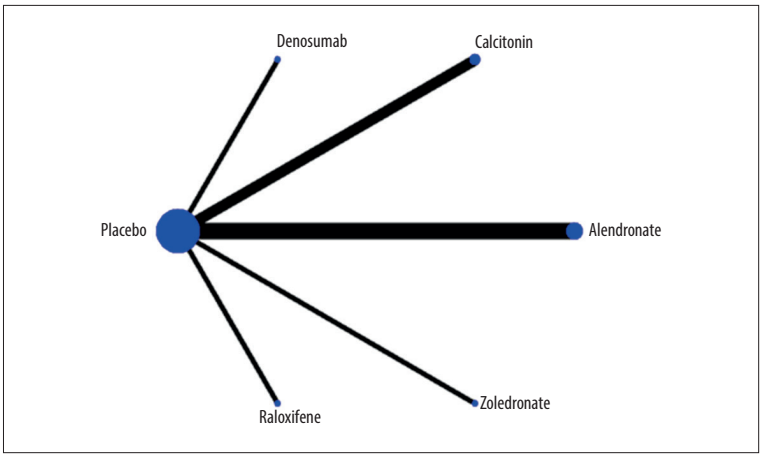
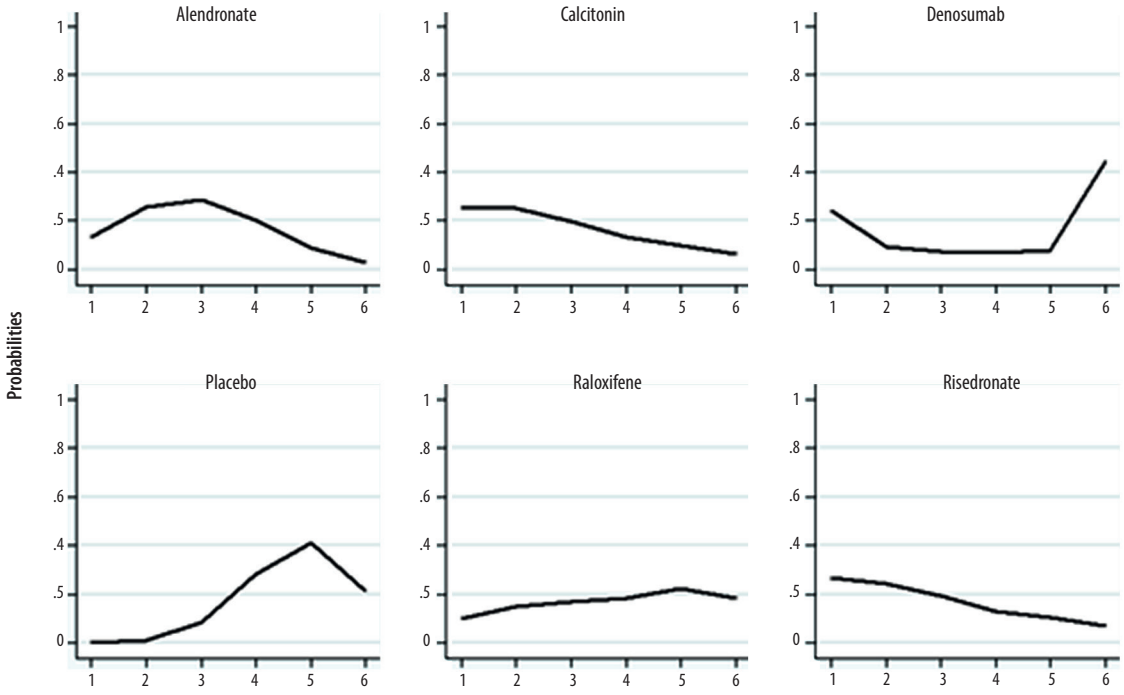
8. Peripheral fracture



Supplementary Figure 8-1. Network of comparisons for peripheral fractures included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
Alendronate	61.0	13.4	3.0
Calcitonin	64.9	25.6	2.8
Denosumab	40.5	2.44	4.0
Placebo	25.5	0.0	4.7
Raloxifene	43.4	9.9	3.8
Zoledronate	64.7	26.6	2.8

Supplementary Figure 8-2. The SUCRA rank test for peripheral fracture.

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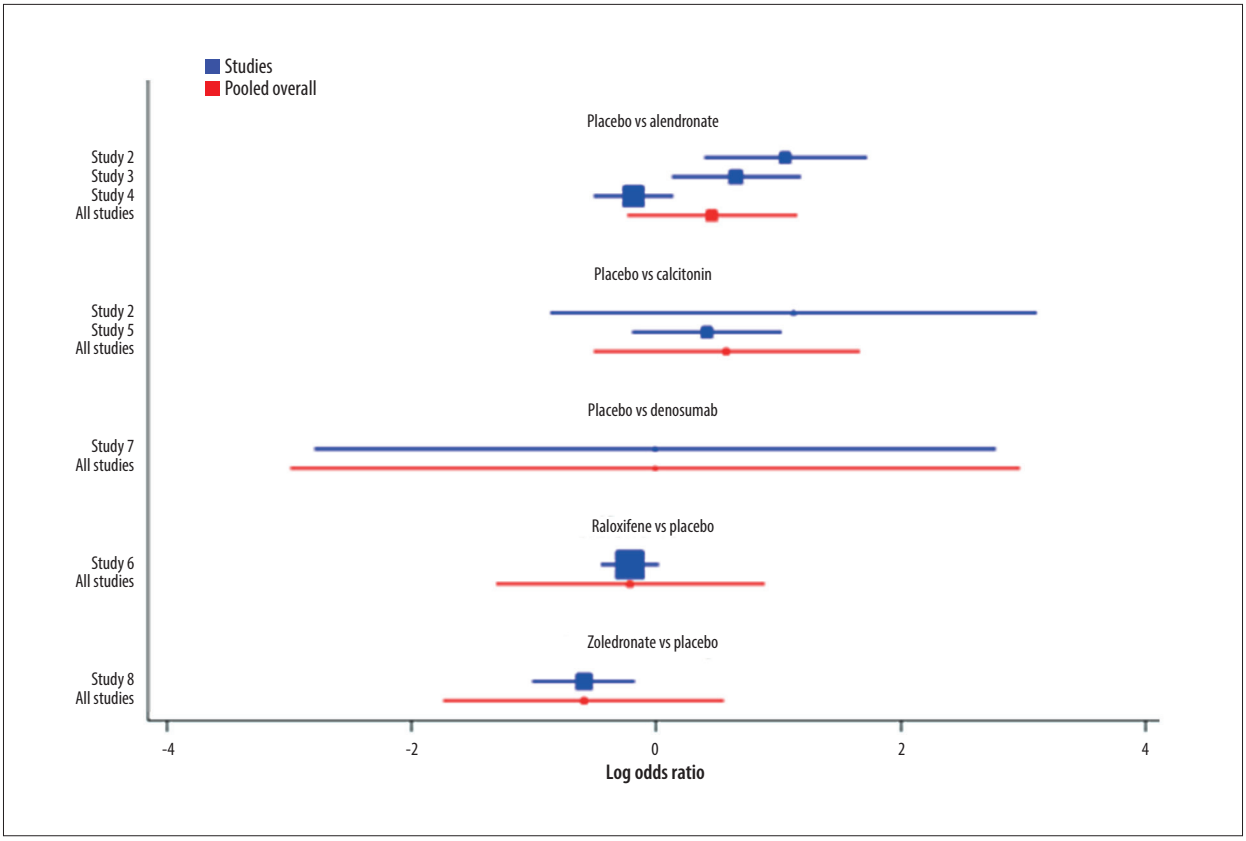
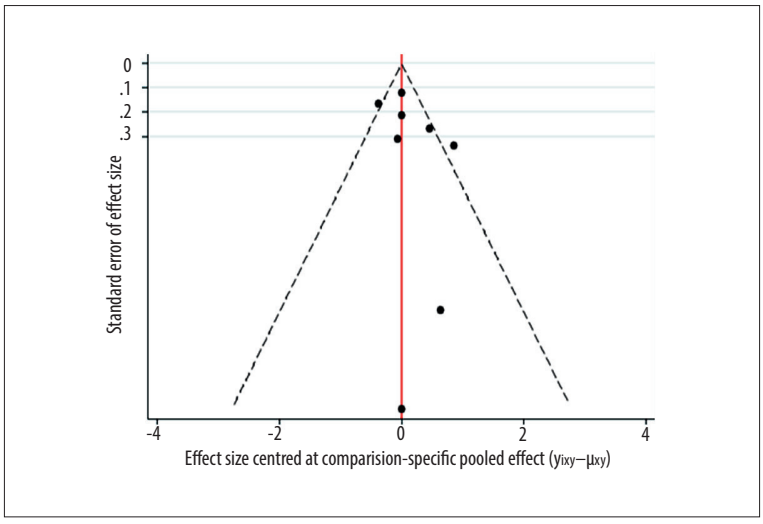


Supplementary Figure 8-3. The pairwise comparisons agents for peripheral fracture.



Supplementary Figure 8-4. Funnel plot for peripheral fracture.

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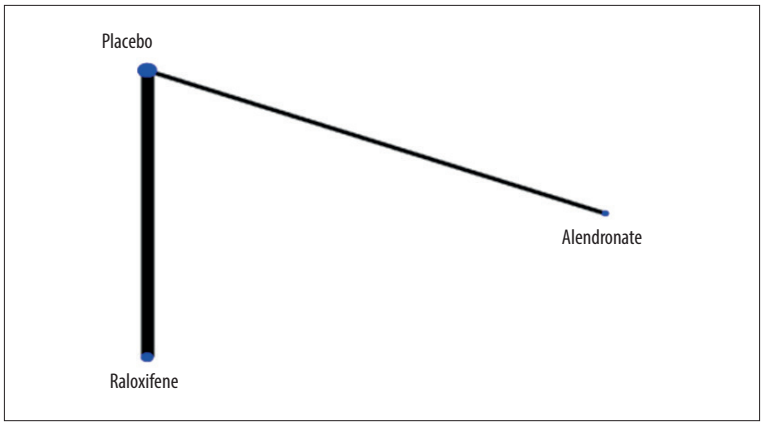
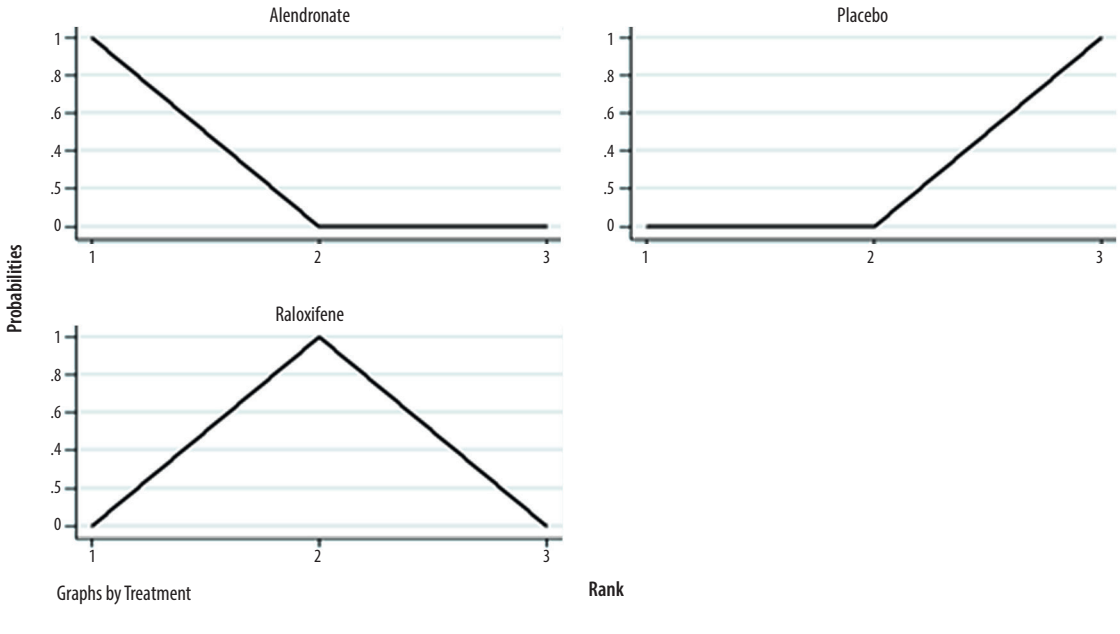
9. Whole-body BMD



Supplementary Figure 9-1. Network of comparisons for whole-body BMD included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
Alendronate	100.0	100.0	1.0
Placebo	0.0	0.0	3.8
Raloxifene	50.0	0.0	2.0

Supplementary Figure 9-2. The SUCRA rank test for whole-body BMD.

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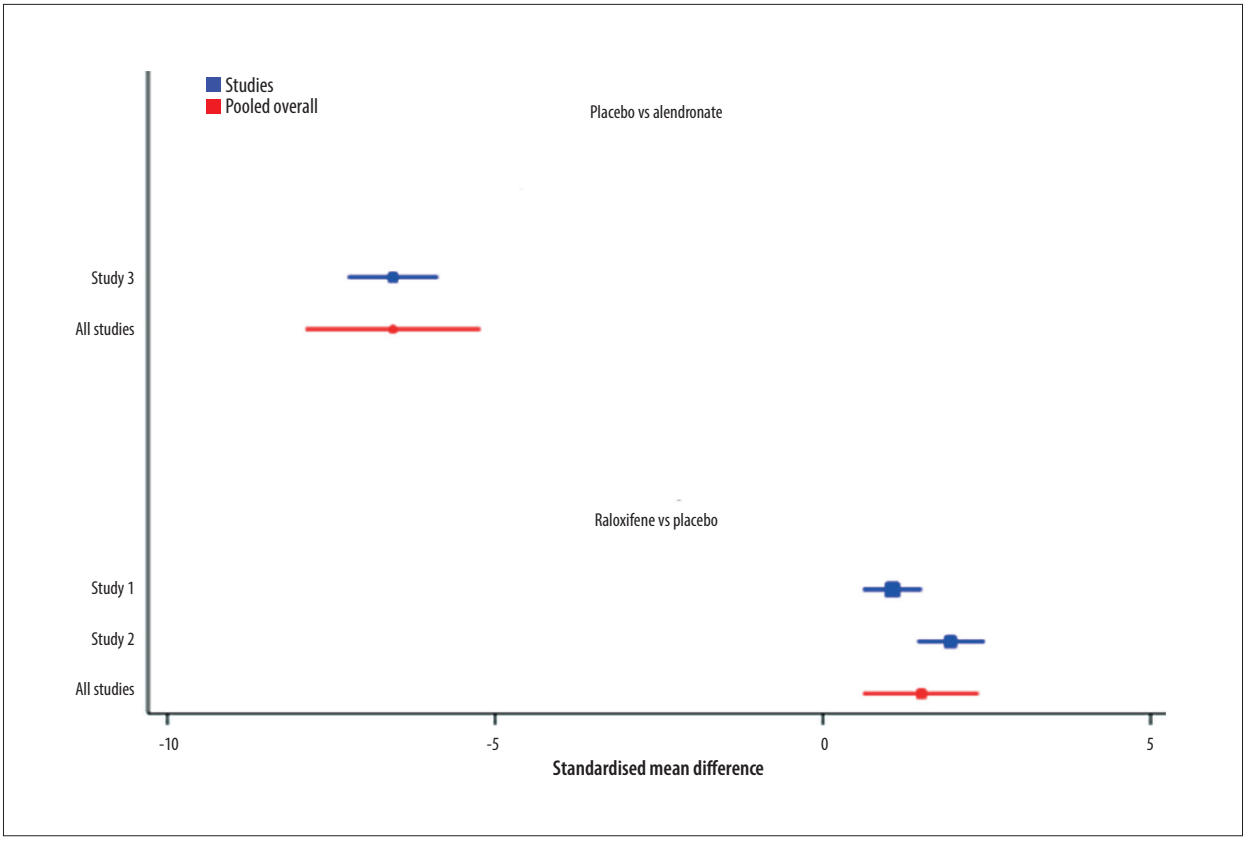
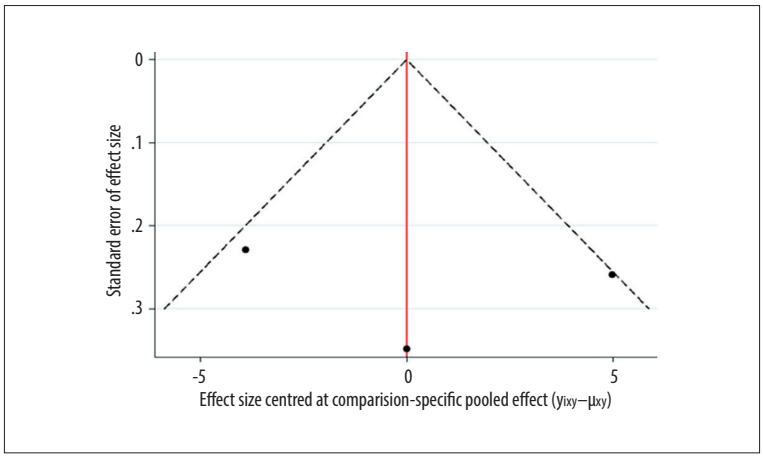


Supplementary Figure 9-3. The pairwise comparisons agents for whole-body BMD.



Supplementary Figure 9-4. Funnel plot for whole-body BMD.

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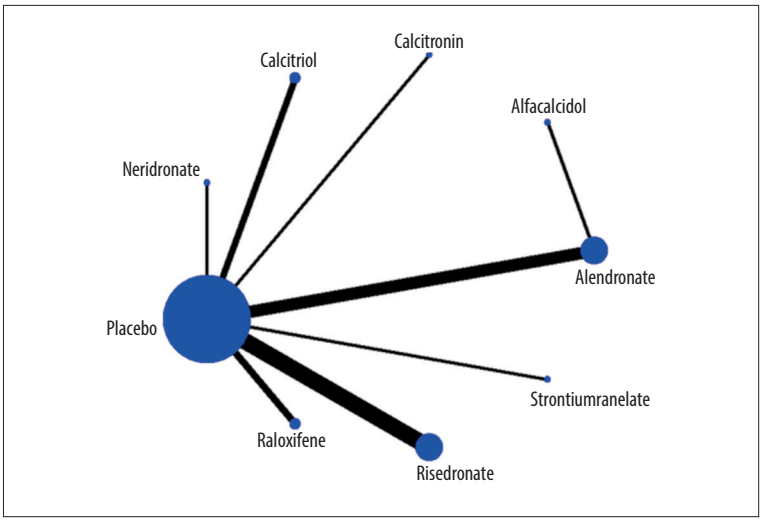
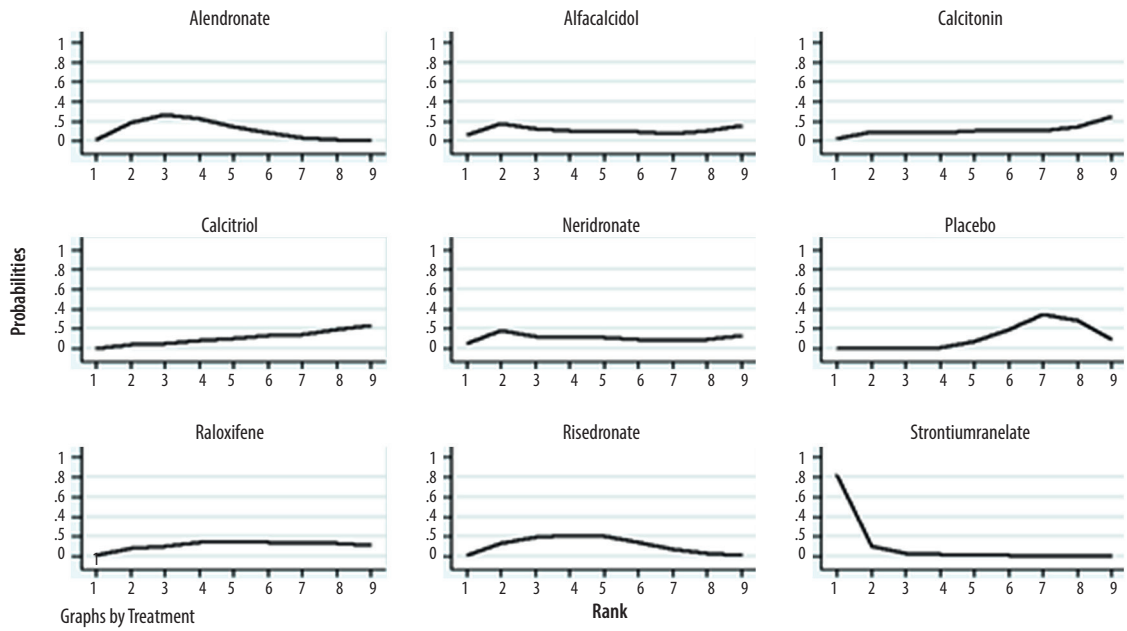
10. Spine BMD



Supplementary Figure 10-1. Network of comparisons for spine BMD included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
Alendronate	64.9	1.8	3.8
Alfacalcidol	49.7	6.5	5.0
Calcitonin	36.2	2.1	6.1
Calcitriol	29.5	0.3	6.6
Neridronate	49.9	4.8	5.0
Placebo	23.5	0.0	7.1
Raloxifene	42.5	1.1	5.6
Risedronate	58.1	1.2	4.3
Strontiumranelate	95.7	82.2	1.3

Supplementary Figure 10-2. The SUCRA rank test for spine BMD.

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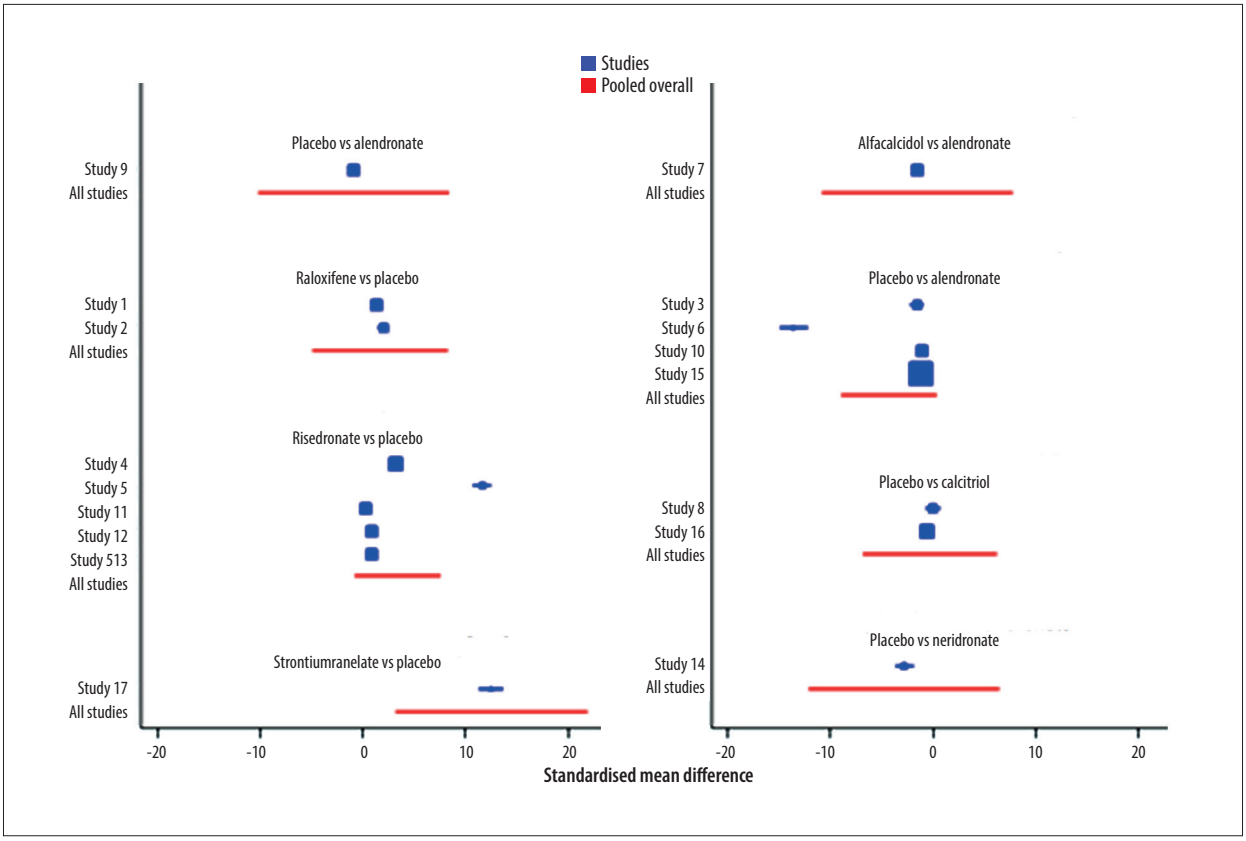
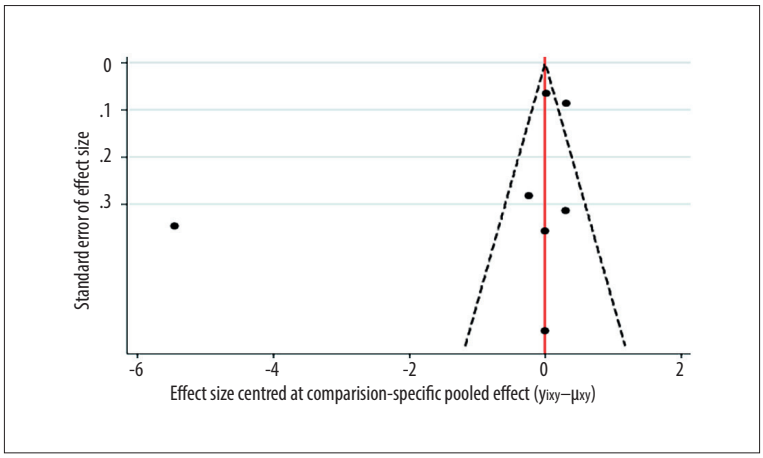


Supplementary Figure 10-3. The pairwise comparisons agents for spine BMD.



Supplementary Figure 10-4. Funnel plot for spine BMD.

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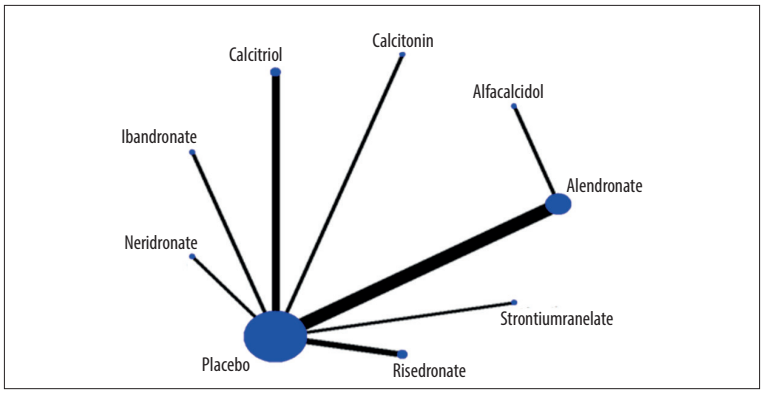
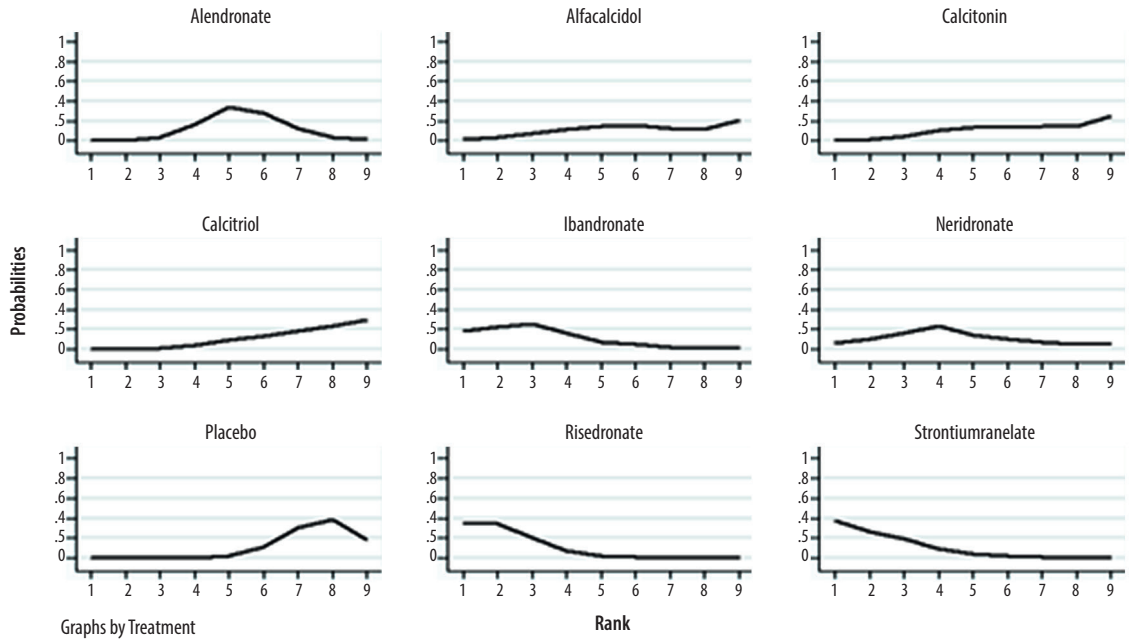
11. Hip BMD



Supplementary Figure 11-1. Network of comparisons for hip BMD included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
Alendronate	45.0	0.0	5.4
Alfacalcidol	35.1	1.5	6.2
Calcitonin	30.2	0.6	6.6
Calcitriol	21.0	0.0	7.3
Ibandronate	73.9	18.4	3.1
Neridronate	56.6	6.4	4.5
Placebo	17.5	0.0	7.6
Risedronate	86.7	35.4	2.1
Strontiumranelate	84.0	37.6	2.3

Supplementary Figure 11-2. The SUCRA rank test for hip BMD.

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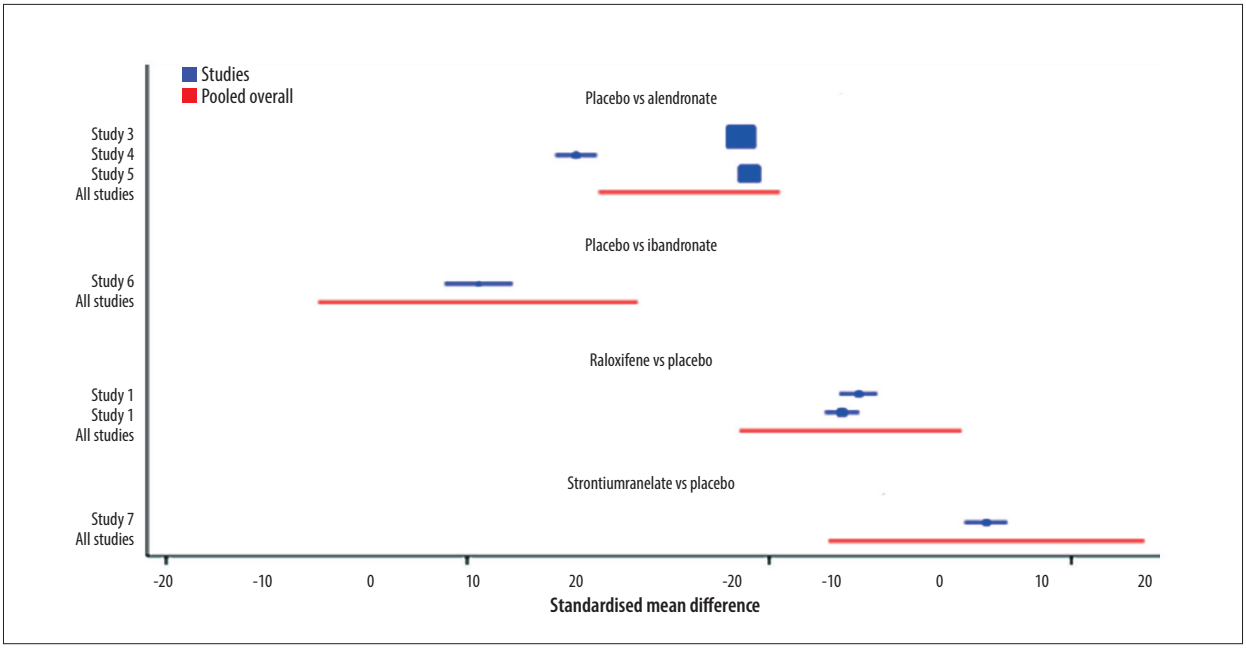
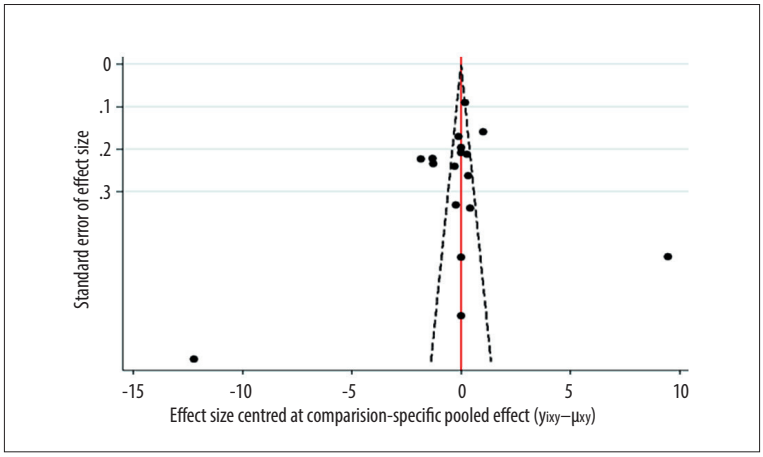


Supplementary Figure 11-3. The pairwise comparisons agents for hip BMD.



Supplementary Figure 11-4. Funnel plot for hip BMD.

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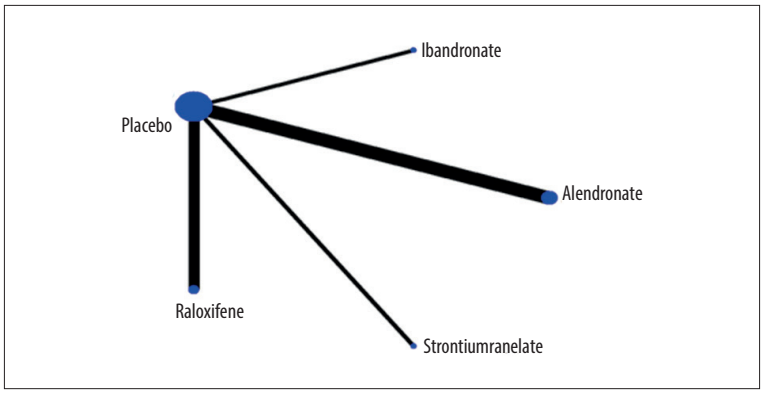
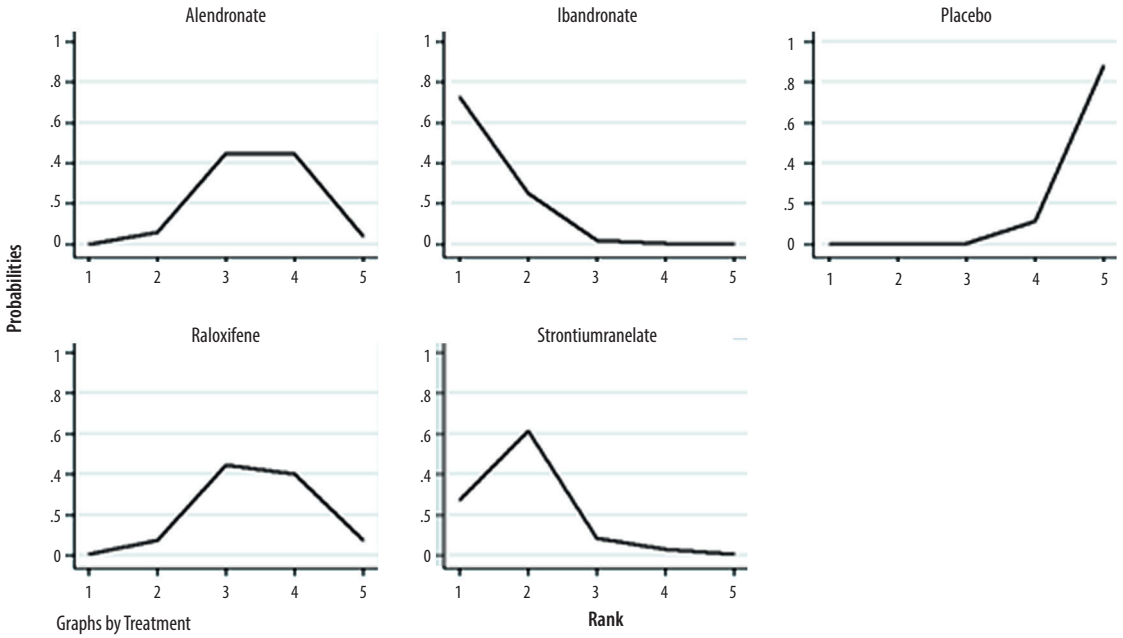
12. Femoral neck BMD



Supplementary Figure 12-1. Network of comparisons for femoral neck BMD included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
Alendronate	38.4	0.1	3.5
Ibandronate	92.4	72.5	1.3
Placebo	3.0	0.0	4.9
Raloxifene	38.3	0.4	3.5
Strontiumranelate	77.9	27.0	1.9

Supplementary Figure 12-2. The SUCRA rank test for femoral neck BMD.

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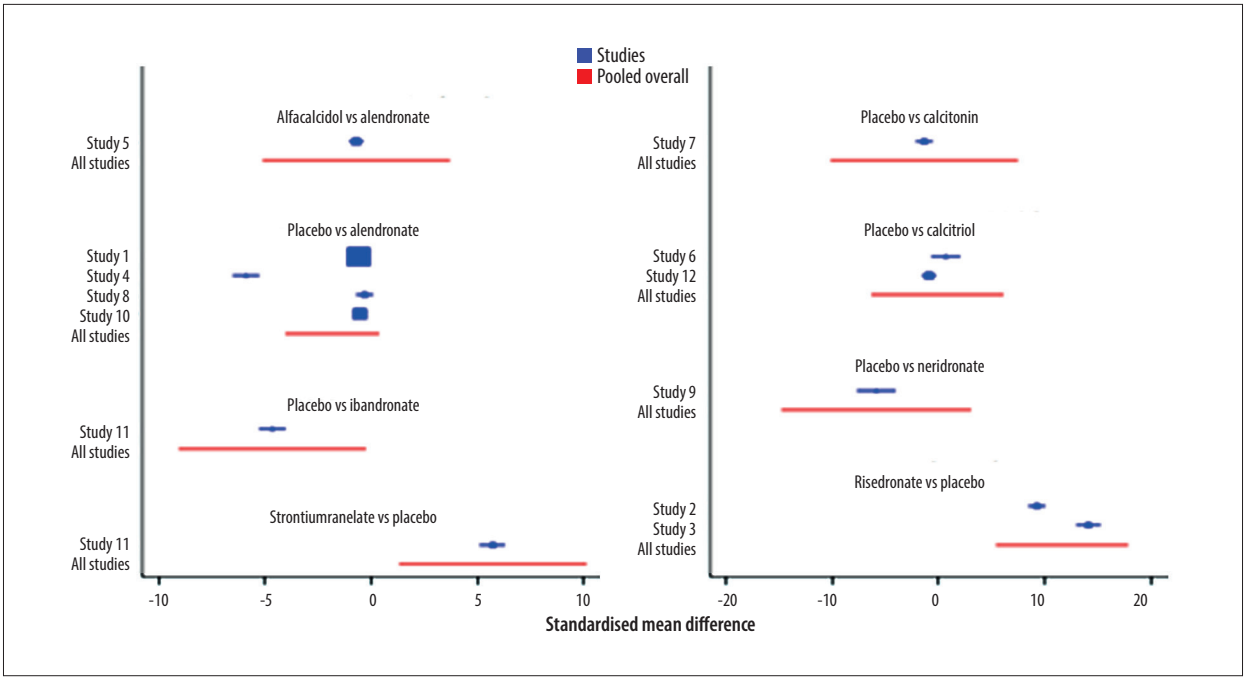
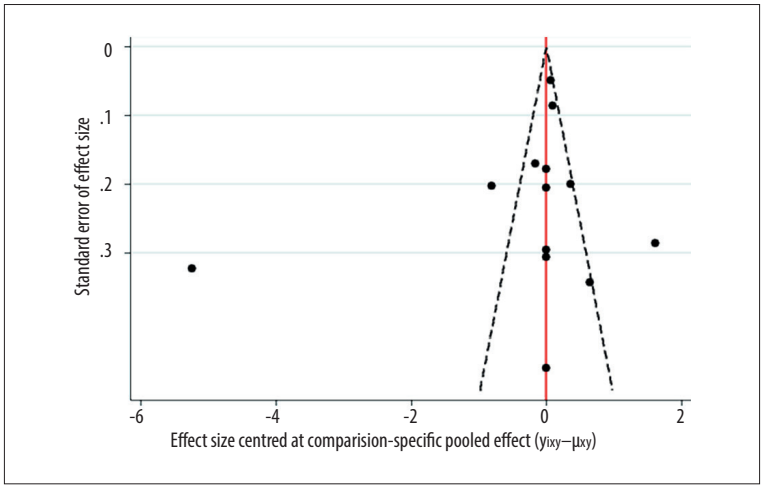


Supplementary Figure 12-3. The pairwise comparisons agents for femoral neck BMD.



Supplementary Figure 12-4. Funnel plot for femoral neck BMD.

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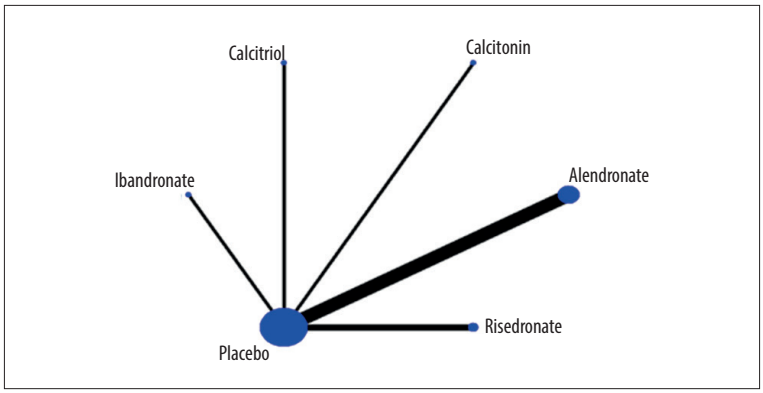
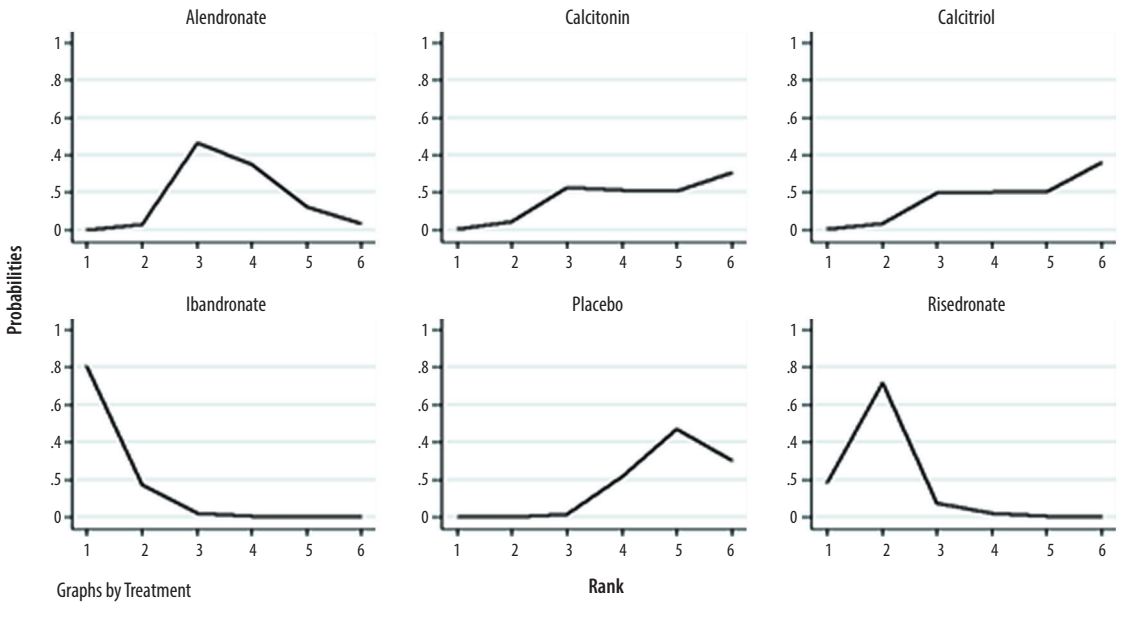
13. Trochanter BMD



Supplementary Figure 13-1. Network of comparisons for trochanter BMD included in the analysis.



Treatment	SUCRA	PrBest	MeanRank
Alendronate	46.9	0.1	3.7
Calcitonin	30.1	0.4	4.5
Calcitriol	27.4	0.6	4.6
Ibandronate	95.5	80.6	1.2
Placebo	18.9	0.0	5.1
Risedronate	81.2	18.4	1.9

Supplementary Figure 13-2. The SUCRA rank test for trochanter BMD.

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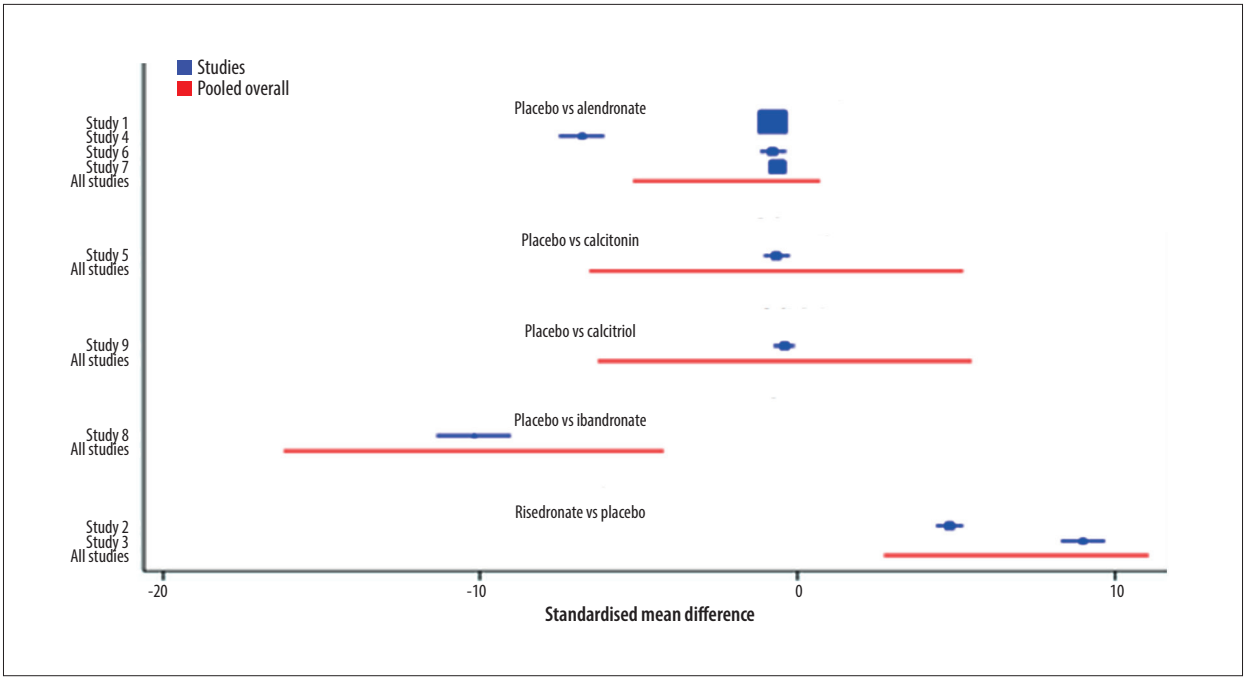
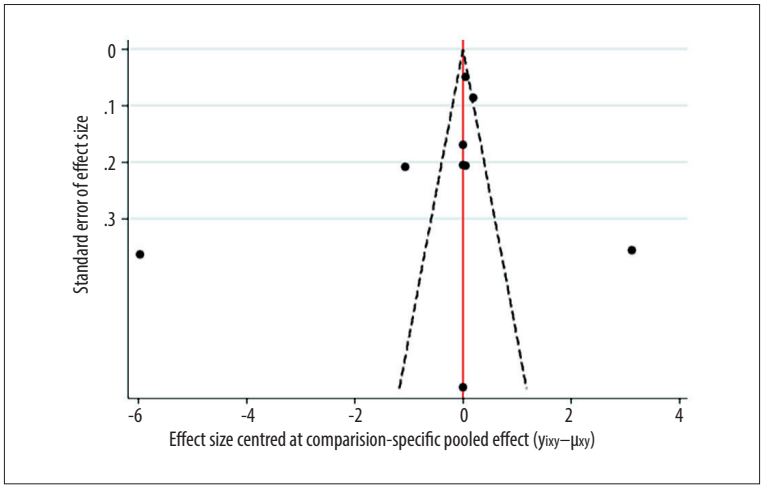


Supplementary Figure 13-3. The pairwise comparisons agents for trochanter BMD.



Supplementary Figure 13-4. Funnel plot for trochanter BMD.

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14. The summary results for adverse events

AEs	Abaloparatide	Alendronate	Alfacalcidol	Bazedoxifene	Calcitonin	Denosumab	Eldecalcitol	Ibandronate
Abdominal pain	–	0.09 (0.07-0.12)	–	0.05 (0.02-0.07)	0.07 (0.06-0.08)	–	–	0.02 (0.02-0.03)
Musculoskeletal pain	–	0.04 (0.03-0.06)	0.02 (-0.01-0.04)	–		0.13 (0.10-0.17)	0.05 (0.01-0.09)	–
Nausea	0.08 (0.06-0.10)	0.06 (0.04-0.08)	0.03 (0.00-0.06)	–	0.15 (0.14-0.17)	0.09 (0.06-0.12)	0.05 (0.01-0.09)	0.05 (0.04-0.06)
Dyspepsia	–	0.07 (0.03-0.10)	–	–	0.10 (0.09-0.11)	0.06 (0.00-0.11)	–	0.06 (0.02-0.10)
Constipation	0.05 (0.03-0.06)	0.03 (0.02-0.05)	0.11 (0.08-0.13)	0.12 (0.08-0.16)	0.07 (0.06-0.08)	0.07 (0.01-0.13)	0.07 (0.05-0.10)	0.07 (-0.02-0.15)
Diarrhea	–	0.04 (0.03-0.04)	0.07 (0.05-0.09)	0.06 (0.04-0.09)	0.07 (0.06-0.08)	0.07 (0.04-0.10)	0.07 (0.01-0.12)	0.05 (0.03-0.06)
Acid regurgitation/ reflux	–	0.05 (0.03-0.08)	–	–	–	0.07 (0.04-0.10)	–	0.05 (0.00-0.10)
Gastritis	–	0.03 (0.02-0.03)	0.04 (0.01-0.08)	0.05 (0.03-0.08)	–	0.04 (-0.00-0.09)	0.05 (-0.00-0.09)	0.02 (0.01-0.02)
Gastric ulcer	–	0.01 (0.00-0.01)	–	–	–	–	–	0.00 (0.00-0.01)
Esophagitis	–	0.01 (0.00-0.01)	–	–	–	–	–	0.01 (0.01-0.02)
Esophageal ulcer	–	0.00 (0.00-0.00)	–	–	–	–	–	0.00 (-0.00-0.00)
Duodenal ulcer	–	0.00 (-0.00-0.00)	–	–	–	–	–	0.00 (-0.00-0.00)
Any upper-gastrointestinal event	–	0.26 (0.16-0.36)	–	0.48 (0.42-0.54)	–	0.02 (0.01-0.03)	0.14 (-0.08-0.36)	0.20 (-0.03-0.43)
Vomiting	–	0.01 (-0.00-0.02)	0.06 (0.04-0.08)	0.04 (0.01-0.06)	0.03 (0.02-0.04)	–	0.06 (0.04-0.09)	0.03 (0.02-0.04)
Influenza syndrome	0.06 (0.05-0.08)	0.04 (0.03-0.06)	–	–	0.06 (0.05-0.07)	0.08 (0.05-0.11)	–	0.06 (0.04-0.07)
Hypertension	0.07 (0.05-0.09)	0.06 (0.05-0.07)	0.07 (0.05-0.09)	–	0.10 (0.09-0.11)	0.05 (0.02-0.07)	0.08 (0.05-0.10)	0.08 (0.06-0.10)
Nasopharingitis	0.06 (0.04-0.07)	0.10 (0.01-0.18)	0.26 (-0.07-0.60)	0.57 (0.51-0.63)	0.17 (0.06-0.27)	0.09 (0.03-0.15)	0.26 (-0.10-0.62)	0.21 (-0.09-0.50)
Headache	0.08 (0.06-0.09)	0.05 (0.03-0.08)	0.07 (0.05-0.10)	0.10 (0.07-0.14)	0.04 (0.03-0.05)	0.05 (-0.02-0.12)	0.07 (0.02-0.12)	–
Nephrolithiasis	–	0.01 (-0.01-0.03)	0.02 (-0.01-0.05)	–	–	–	0.01 (0.00-0.02)	–
Myalgia	–	0.04 (0.01-0.07)	–	–	–	0.06 (0.00-0.11)	–	0.06 (0.01-0.12)
Pyrexia	–	0.05 (0.02-0.09)	–	–	–	–	–	–
Arthralgia	0.09 (0.07-0.11)	0.07 (0.04-0.11)	0.09 (0.07-0.12)	0.14 (0.10-0.18)	0.12 (0.11-0.14)	0.07 (0.02-0.12)	0.10 (0.08-0.12)	0.09 (0.04-0.14)
Blood calcium increased	–	-	0.09 (0.03-0.15)	–	–	–	0.11 (0.03-0.19)	–

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AEs	Abaloparatide	Alendronate	Alfacalcidol	Bazedoxifene	Calcitonin	Denosumab	Eldecalcitol	Ibandronate
Urine calcium increased	–	0.04 (-0.00-0.09)	0.07 (0.00-0.15)	–	–	–	0.11 (0.01-0.22)	–
Back pain	0.09 (0.07-0.10)	0.13 (0.03-0.22)	0.12 (0.06-0.19)	0.18 (0.13-0.22)	0.13 (0.12-0.15)	0.08 (0.03-0.13)	0.12 (0.08-0.16)	0.09 (0.02-0.16)
Urinary tract infection	0.05 (0.04-0.07)	0.07 (-0.01-0.14)	0.10 (0.05-0.16)	–	–	0.08 (0.05-0.11)	0.08 (0.04-0.13)	0.02 (0.01-0.02)

AEs	Lasofoxifene	Neridronate	Raloxifene	Risedronate	Romosozumab	Strontium ranelate	Zoledronate
Abdominal pain	–	–	0.07 (0.00-0.13)	0.10 (0.08-0.12)	–	-	-
Musculoskeletal pain	–	–	–	0.01 (-0.01-0.02)	–	-	0.13 (0.00-0.26)
Nausea	–	–	0.03 (0.02-0.04)	0.04 (0.01-0.07)	–	0.04 (-0.00-0.08)	0.09 (0.06-0.12)
Dyspepsia	–	–	–	0.10 (0.08-0.12)	–	-	-
Constipation	–	–	–	0.05 (-0.00-0.11)	–	0.05 (0.00-0.10)	0.07 (0.03-0.11)
Diarrhea	–	–	0.02 (0.01-0.03)	0.01 (-0.01-0.03)	–	0.07 (0.04-0.11)	0.05 (0.01-0.08)
Acid regurgitation/ reflux	–	–	–	-	–	–	0.02 (-0.00-0.04)
Gastritis	–	–	–	0.03 (0.01-0.04)	–	–	–
Gastric ulcer	–	–	–	0.01 (0.00-0.01)	–	–	–
Esophagitis	–	–	–	0.02 (0.01-0.02)	–	–	–
Esophageal ulcer	–	–	–	0.00 (0.00-0.01)	–	–	–
Duodenal ulcer	–	–	–	0.01 (0.00-0.01)	–	–	–
Any upper-gastrointestinal event	–	–	0.13 (0.08-0.17)	0.19 (0.14-0.25)	–	0.05 (0.00-0.10)	–
Vomiting	–	–	–	–	–	–	–
Influenza syndrome	–	0.55 (0.33-0.77)	0.13 (0.13-0.14)	0.06 (0.02-0.09)	–	–	0.04 (0.01-0.07)
Hypertension	–	–	0.07 (0.07-0.08)	0.03 (0.02-0.05)	–	0.10 (0.06-0.15)	0.08 (0.06-0.10)
Nasopharingitis	–	–	–	0.06 (0.03-0.09)	0.17 (0.14-0.19)	-	0.22 (-0.04-0.47)
Headache	–	–	–	0.05 (0.02-0.08)	–	0.03 (-0.01 to 0.06)	0.09 (0.03-0.15)
Nephrolithiasis	–	–	–	–	–	0.03 (-0.01-0.07)	–
Myalgia	–	–	–	–	–	–	0.10 (0.04-0.17)

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AEs	Lasofoxifene	Neridronate	Raloxifene	Risedronate	Romosozumab	Strontium ranelate	Zoledronate
Pyrexia	–	–	–	–	–	–	0.15 (0.07-0.24)
Arthralgia	0.26 (0.25-0.27)	–	–	0.06 (0.04-0.07)	0.16 (0.15-0.18)	0.06 (0.03-0.08)	0.13 (0.05-0.21)
Blood calcium increased	–	–	–	–	–	–	–
Urine calcium increased	–	–	–	–	–	0.06 (0.03-0.10)	–
Back pain	–	–	–	0.05 (0.03-0.07)	0.15 (0.11-0.18)	0.09 (0.05-0.13)	0.10 (0.05-0.16)
Urinary tract infection	–	–	–	–	–	–	–

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