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Drug efficacy and safety of denosumab, teriparatide, zoledronic acid, and ibandronic acid for the treatment of postmenopausal osteoporosis: a network meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: This study aims to compare the efficacy and safety of denosumab, teriparatide, zoledronic acid, and ibandronic acid for the treatment of women with postmenopausal osteoporosis.

MATERIALS AND METHODS: Randomized controlled trials (RCTs) were searched in Medline, Embase, and Cochrane up to April 2022. Statistical analysis was performed using R 4.1.3 software, and quality evaluation was conducted using Review Manager 5.3.

RESULTS: 51 RCTs containing 39,095 patients met our selection criteria. The efficacy results indicated that teriparatide was more effective than ibandronic acid in reducing vertebral fractures [relative risk (RR) = 0.536; 95% confidence interval (CI) (0.266, 0.998)]. Denosumab [mean difference (MD) = -4.19; 95% CI (-8.03, -0.355)] and teriparatide [MD = 4.64; 95% CI (1.60, 7.72)] showed better efficacy than ibandronic acid in improving spine bone mineral density (BMD). Denosumab showed better efficacy than teriparatide in improving radius BMD [MD = -4.14; 95% CI (-6.72, -1.54)], hip bone mineral density (BMD) [MD = -2.01; 95% CI (-3.80, -0.162)], and one-third radius BMD [MD = -3.63; 95% CI (-7.04, -0.151)]. Denosumab was associated with the greatest benefit in increasing radius BMD [the surface under the cumulative ranking curve area (SUCRA) = 0.999], hip BMD [surface under the cumulative ranking curve area (SUCRA) = 0.979], femoral neck BMD (SUCRA = 0.971), one-third radius BMD (SUCRA = 0.994) and preventing vertebral fractures (SUCRA = 0.806). Teriparatide was associated with the greatest benefit in preventing non-vertebral fractures (SUCRA = 0.927) and improving spine BMD (SUCRA = 0.899). The safety results indicated that teriparatide was safer than zoledronic acid regarding the risk of adverse events [RR = 0.958; 95% CI (0.919, 0.988)]. Teriparatide was associated with the greatest benefit in preventing adverse events (SUCRA = 0.908) and serious adverse events (SUCRA = 0.813).

CONCLUSIONS: Our current results suggested that when considering both safety and efficacy, denosumab or teriparatide might be a better choice for women with postmenopausal osteoporosis.

Key Words:
Postmenopausal, Osteoporosis, Denosumab, Teriparatide, Zoledronic acid, Ibandronic acid.

Abbreviations

randomized controlled trials (RCTs); bone mineral density (BMD); the surface under the cumulative ranking curve area (SUCRA); relative risk (RR); confidence interval (CI); mean difference (MD); standard mean difference (SMD); standard error of the mean (SEM); standard deviation (SD); alkaline phosphatase (ALP), N-telopeptide of type I collagen (NTX).

Introduction

Postmenopausal women with lower estrogen levels experience accelerated bone resorption and inhibited bone formation, leading to low bone mass. Postmenopausal osteoporosis is characterized by a metabolic disorder in the skeleton, resulting in low bone mineral density (BMD), high bone fragility, and microarchitectural atrophy in the bone tissue, which increase the risk of fractures, such as vertebrae, femur, and distal forearm fractures[1,2]. Furthermore, vitamin D deficiency and unhealthy lifestyle

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habits, such as smoking, alcohol consumption, and inadequate intake of trace elements and nutrients, have been identified as potentially modifiable risk factors for osteoporosis[3]. Osteoporosis affects approximately 200 million patients worldwide, contributing to over 8.9 million fractures each year[4]. In the United States and Europe, about 30% of all postmenopausal women have osteoporosis. Among Chinese women over 50 years old, the age-standardized prevalence of osteoporosis is 29.13%[5]. Our previous studies[6,7] have shown that patients with postmenopausal osteoporosis face significant challenges, including frailty, limited mobility, dependence on others, and increased mortality risk, along with significant economic burdens. Therefore, there is a clinical need to analyze and select safe and effective anti-osteoporosis drugs for the treatment of postmenopausal osteoporosis.

Pharmacologic therapy is commonly used as the first-line treatment for patients with osteoporosis. According to guidelines[8,9], zoledronic acid and ibandronic acid are commonly used as first-line therapies due to their therapeutic effects in inhibiting bone resorption[10]. Denosumab, by reducing osteoclast activity, is considered a good alternative[11]. Teriparatide, a parathormone analogue that stimulates osteoblast activity, can rapidly reduce the incidence of fractures in high-risk populations[10,12,13]. Our previous study[7] found that denosumab treatment was cost-effective compared to teriparatide, zoledronate, or ibandronate. However, effectiveness and safety are both crucial factors to consider in clinical therapy selection. It is necessary to identify an effective and long-term safe treatment to prevent bone loss and reduce the risk of fractures in osteoporosis patients.

Previous meta-analyses[7,14] have been conducted to determine the most effective therapy, but the conclusions have been controversial. A network meta-analysis[7] demonstrated that denosumab was superior to zoledronic acid or ibandronic acid in reducing vertebral fractures, and teriparatide was more effective than ibandronate in preventing non-vertebral fractures. However, another study[14] showed no significant difference among denosumab, ibandronic acid, zoledronic acid, and teriparatide. In terms of safety assessment, it is well-known that pharmacologic therapy for osteoporosis can lead to adverse events such as cardiovascular disease, metabolic and nutritional disorders, back pain, cancer, and hypocalcemia[15-19]. Likewise, long-term administration of bisphosphonates like zoledronic acid has been reported to cause gastrointestinal disturbances[20,21]. Based on this background, a meta-analysis that assesses both efficacy and safety of anti-osteoporosis drugs is of great clinical importance.

Therefore, we conducted a network meta-analysis of randomized controlled trials (RCTs) to compare the efficacy and safety of denosumab, zoledronic acid, ibandronic acid, and teriparatide in women with postmenopausal osteoporosis. We evaluated ten outcomes, including vertebral fracture, non-vertebral fracture, spine BMD, hip BMD, femoral neck BMD, one-third radius BMD, radius BMD, adverse events, serious adverse events, and drug-related adverse events, in order to provide reliable clinical therapy guidelines.

Materials and Methods

We implemented this meta-analysis based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (**PRISMA**) guidelines[22]. This study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD42022362530.

Search Strategy

Two authors conducted a literature search in three databases: PubMed, Embase, and Cochrane Library. The search was conducted on April 7th, 2022, with no limitation on publication year. The search terms included: (1) postmenopausal osteoporosis; (2) denosumab, teriparatide, zoledronic acid, and ibandronic acid; (3) synonyms for the above terms. The search strategy was demonstrated in **Supplementary Table I**.

Eligibility Criteria and Study Selection

Inclusion criteria: (1) RCTs; (2) study subjects were women with postmenopausal osteoporosis; (3) interventions included at least two kinds of drugs among placebo, denosumab, teriparatide, zoledronic acid, and ibandronic acid; (4) subjects were not intervened with other anti-osteoporosis drugs besides the four mentioned treatments; (5) outcomes included at least one of the following: vertebral fracture, non-vertebral fracture, spine BMD, total hip BMD, femoral neck BMD, one-third radius BMD, radius BMD, adverse events, serious adverse events, and drug-related adverse events; (6) mean values and standard deviation could be calculated for BMD-related outcomes, and the number of events could be calculated for vertebral fracture, non-vertebral fracture, adverse events, serious adverse events, and drug-related adverse events.

Exclusion criteria: (1) duplicate studies; (2) reviews or meta-analyses; (3) study subjects were men or women without postmenopausal osteoporosis; (4) subjects received other anti-osteoporosis drugs during the intervention period; (5) studies that did not report the specified outcomes or provide usable data; (6) full text of the study could not be found.

Two researchers independently selected articles based on titles, abstracts, and final full-text readings were conducted to include or exclude studies. In case of disagreements between the two researchers, a third reviewer participated in the assessment, and decisions were made through group discussion.

Data Extraction

Essential information, including title, published year, authors, sample size, years since menopause, country, intervention periods, age, and other supplementary interventions were extracted. The outcomes of interest were vertebral fracture, non-vertebral fracture, spine BMD, total hip BMD, femoral neck BMD, one-third radius BMD, radius BMD, adverse events, serious adverse events, and drug-related adverse events. If authors provided percentages instead of exact numbers, they were transformed into precise values. Additionally, the standard error of the mean (SEM) was converted to standard deviation (SD), and changes between groups were calculated to obtain more useful data for evaluating the four anti-osteoporosis drugs. Data extraction was performed independently by two authors, with discrepancies resolved through discussion with a third reviewer (**Supplementary Table II**).

Quality Assessment and Bias Evaluation

All included studies were independently assessed for risk of bias using the Cochrane Risk of Bias tool by two authors. The criteria included: (1) Random Sequence Generation; (2) Allocation Concealment; (3) Blinding of Participants; (4) Blinding of Outcome Assessment; (5) Incomplete Outcome Data; (6) Selective Reporting; (7) Other Sources of Bias. The risk of bias was indicated by a green background and a "+" symbol for low risk, a red background and a "-" symbol for high risk, and a yellow background and a "?" symbol for unclear risk (**Supplementary Figure 1**).

Statistical Analysis

The direct, indirect, and network meta-analyses were conducted using R ×64 4.1.3 (R Core Team 2022, R Foundation for Statistical Computing, Vienna, Austria), RStudio (Boston, MA, USA) and JAGS 4.3.0 (Cambridge, UK). The packages we used in R 4.1.3 software include Rtools 4.0, xlsx, gemtc, rjags, nloptr. Quality assessment was performed using RevMan 5.3 version software (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark). The random-effects or fixed-effects model was selected based on the I^2 values, and the two-sided $p < 0.05$ was considered statistically significant. Relative risk (RR) and 95% confidence interval (CI) were calculated for dichotomous data, and mean difference (MD) and 95% CI were calculated for continuous variables. In this study, dichotomous variables included adverse events, serious adverse events, drug-related adverse events, vertebral fracture, and non-vertebral fracture, while continuous variables included spine BMD, hip BMD, femoral neck BMD, one-third radius BMD, and radius BMD. MD was chosen for continuous variables since it provided clearer quantitative results without requiring standardization. Heterogeneity was assessed using I^2 values (**Supplementary Figure 2**), with $I^2 > 50\%$ considered significant heterogeneity. Inconsistency was assessed using node split analysis, with $p < 0.05$ considered a significant difference. This indicates the presence of inconsistency of comparison among direct, indirect and network (**Supplementary Figure 3**). To reflect the rank and uncertainty, the surface under the cumulative ranking curve area (SUCRA) was presented to rank the four treatments, with higher values indicating better efficacy or fewer adverse events. SUCRA was used to determine the relative probability of each intervention being one of the best choices.

Results

Study Characteristics

The flowchart of study and inclusion results are described in Figure 1. We searched a total of 5,330 potential articles and ultimately included 51 RCTs[15-17,23-70] (Figure 1), involving 39,095 patients over the age of 42. Most subjects received daily calcium and vitamin D supplementation. When evaluating the full articles, we excluded a total of 18 articles. These exclusions included 1 article involving osteoporosis patients with other disease[71], 14 articles that lacked available data[72-85], 2 articles[86,87] comparing risedronate *vs.* teriparatide and risedronate *vs.* ibandronic acid, as well

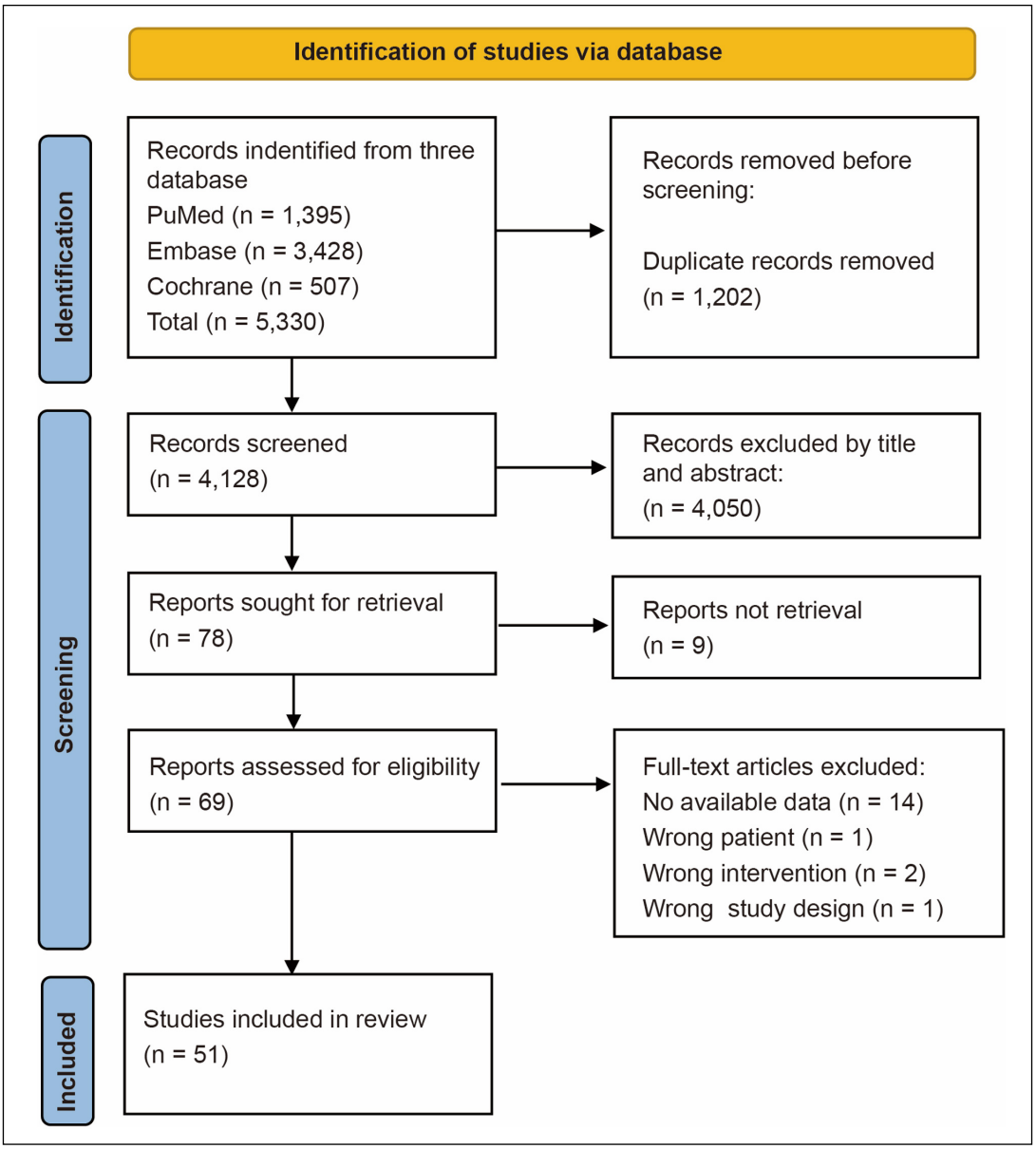

Figure 1. PRISMA Flow Diagram.

as 1 study[88] comparing the cyclic (three separate 12-month cycles of 6 months of teriparatide followed by 6 months of denosumab) or standard (18 months of teriparatide followed by 18 months of denosumab) treatment of teriparatide and denosumab. The included studies compared denosumab *vs.* placebo (n = 8)[17,24,29,40,44,50,52,57], denosumab *vs.* teriparatide (n = 3)[42,43,69], ibandronic acid *vs.* placebo (n = 12)[16,25,28,33,49,53,61,62,64,66-68], teriparatide *vs.* placebo (n =16)[30,32,34,36,37,39,41,46,47,51,54-56,58,65,70], teriparatide *vs.* zoledronic acid (n = 2)[15,35], and zoledronic acid *vs.* placebo (n = 10)[23,26,27,31,38,45,48,59,60,63]. **Supplementary Table II** provides detailed information on the included studies. The risk bias of included RCTs is shown in Figure 2 and **Supplementary Figure 1**.

Efficacy

The primary efficacy outcome was vertebral fracture, and the secondary outcomes included non-vertebral fracture, changes in spine BMD, total hip BMD, femoral neck BMD, one-third radius BMD, and radius BMD. The results are described below.

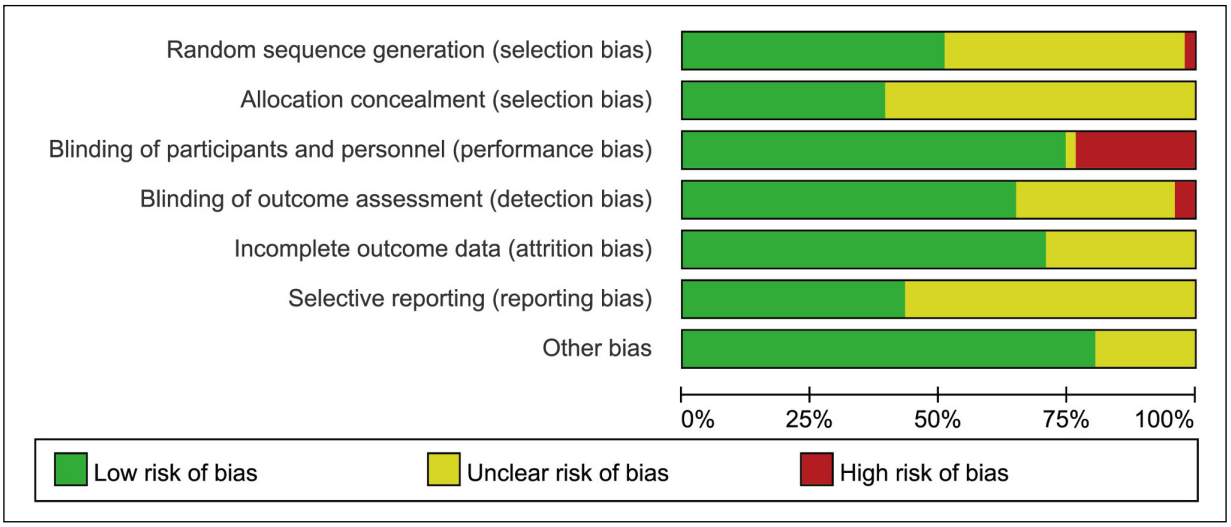

Figure 2. Risk of bias.

Vertebral Fracture

Thirteen[17,26,27,30,31,33,38,47,54,55,58,59,61] RCTs reported vertebral fracture outcomes (denosumab *vs.* placebo n = 1[17]; zoledronic acid *vs.* placebo n = 5[26,27,31,38,59]; ibandronic acid *vs.* placebo n = 2[33,61]; teriparatide *vs.* placebo n = 5[30,47,54,55,58]). Compared with placebo, denosumab [RR = 0.325; 95% CI (0.149, 0.706)], zoledronic acid [RR = 0.353; 95% CI (0.218, 0.593)], and teriparatide [RR = 0.360; 95% CI (0.238, 0.505)] significantly reduced the incidence of vertebral fractures. Teriparatide [RR = 0.536; 95% CI (0.266, 0.998)] was also more effective than ibandronic acid in preventing vertebral fractures. The ranking based on SUCRA values for vertebral fracture was as follows: denosumab (SUCRA = 0.806) > zoledronic acid (SUCRA = 0.723) > teriparatide (SUCRA = 0.709) > ibandronic acid (SUCRA = 0.257) > placebo (SUCRA = 0.005) (Figure 3).

Non-Vertebral Fracture

Figure 4 showed the results for non-vertebral fractures based on 8[17,29-31,33,54,55,59] RCTs (denosumab *vs.* placebo n = 2[17,29]; zoledronic acid *vs.* placebo n = 2[31,59]; ibandronic acid *vs.* placebo n = 1[33]; teriparatide *vs.* placebo n = 3[30,54,55]). Only teriparatide [RR = 0.528; 95% CI (0.276, 0.982)] significantly reduced the risk of non-vertebral fractures compared to placebo. The ranking based on SUCRA values for non-vertebral fracture was as follows: teriparatide (SUCRA = 0.927) > zoledronic acid (SUCRA = 0.659) > denosumab (SUCRA = 0.561) > placebo (SUCRA = 0.222) > ibandronic acid (SUCRA = 0.132).

Spine BMD

Twenty-three[16,23,28,29,32,33,37,39,41-43,45,48,50,51,56,58,60,64,65,66,68,69] RCTs reported the effect of the four drugs on changes in spine BMD (denosumab *vs.* placebo n = 2[50,29]; zoledronic acid *vs.* placebo n = 4[23,45,48,60]; ibandronic acid *vs.* placebo n = 6[16,28,33,64,66,68]; teriparatide *vs.* placebo n = 8[42,37,39,41,51,56,58,65]; denosumab *vs.* teriparatide n = 3[42,43,69]). All four anti-osteoporosis drugs significantly increased spine BMD compared to placebo, and both teriparatide [MD = 4.64; 95% CI (1.60, 7.72)] and denosumab had a greater effect on increasing spine BMD compared to ibandronic acid. The ranking based on SUCRA values for spine BMD was as follows: teriparatide (SUCRA = 0.899) > denosumab (SUCRA = 0.823) > zoledronic acid (SUCRA = 0.478) > ibandronic acid (SUCRA = 0.3) > placebo (SUCRA = 0) (Figure 5).

Total Hip BMD

Seventeen[16,23,28,29,33,34,41,42,43,45,48,49,50,56,58,68,69] RCTs reported the effect of the four drugs on total hip BMD. The forest plot is shown in **Supplementary Figure 4**. All four treatments significantly increased total hip BMD compared to placebo. Furthermore, there was a statistically significant difference between teriparatide and denosumab, with teriparatide [MD = -2.01; 95% CI (-3.80, -0.162)] being inferior. The ranking based on SUCRA values for total hip BMD was as follows: denosumab (SUCRA = 0.979) > zoledronic acid (SUCRA = 0.57) > teriparatide (SUCRA = 0.494) > ibandronic acid (SUCRA = 0.457) > placebo (SUCRA = 0).

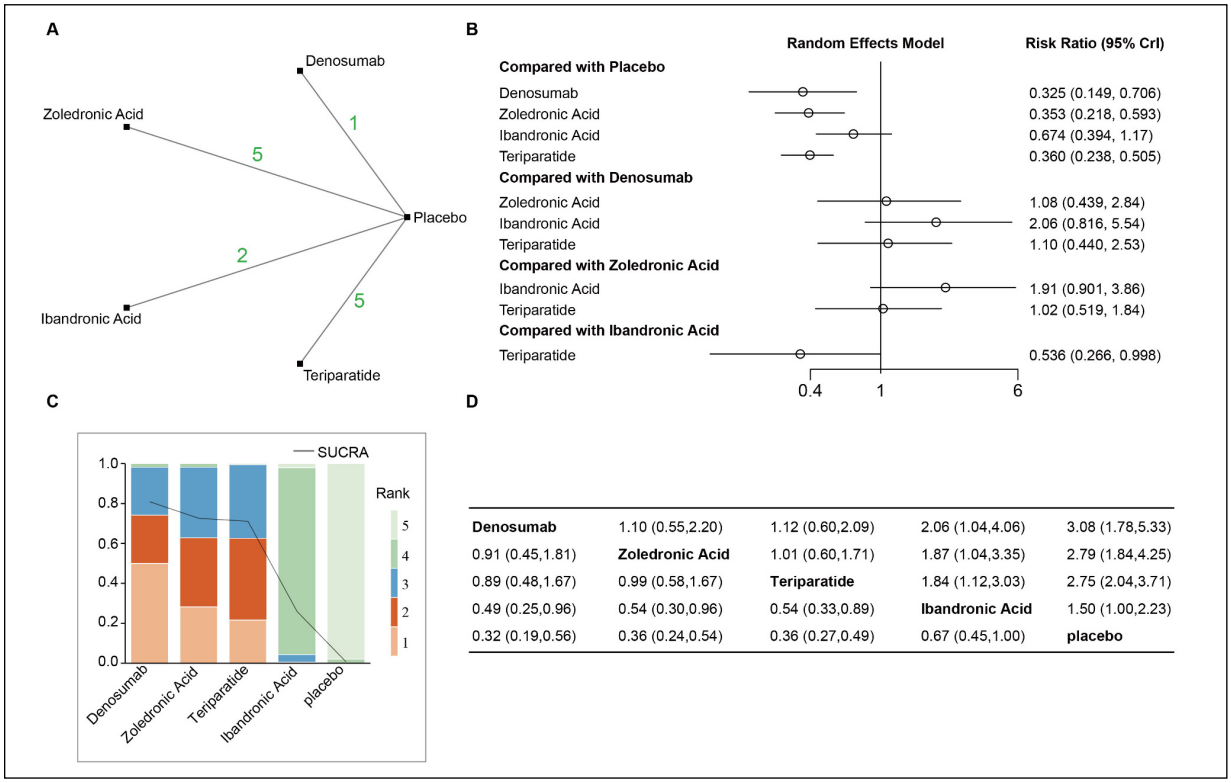

Figure 3. Summary of network meta-analysis of vertebral fracture outcomes. **A**, The network plots. **B**, Forest map of network comparison. **C**, Cumulative probability rank. **D**, Net-league table.

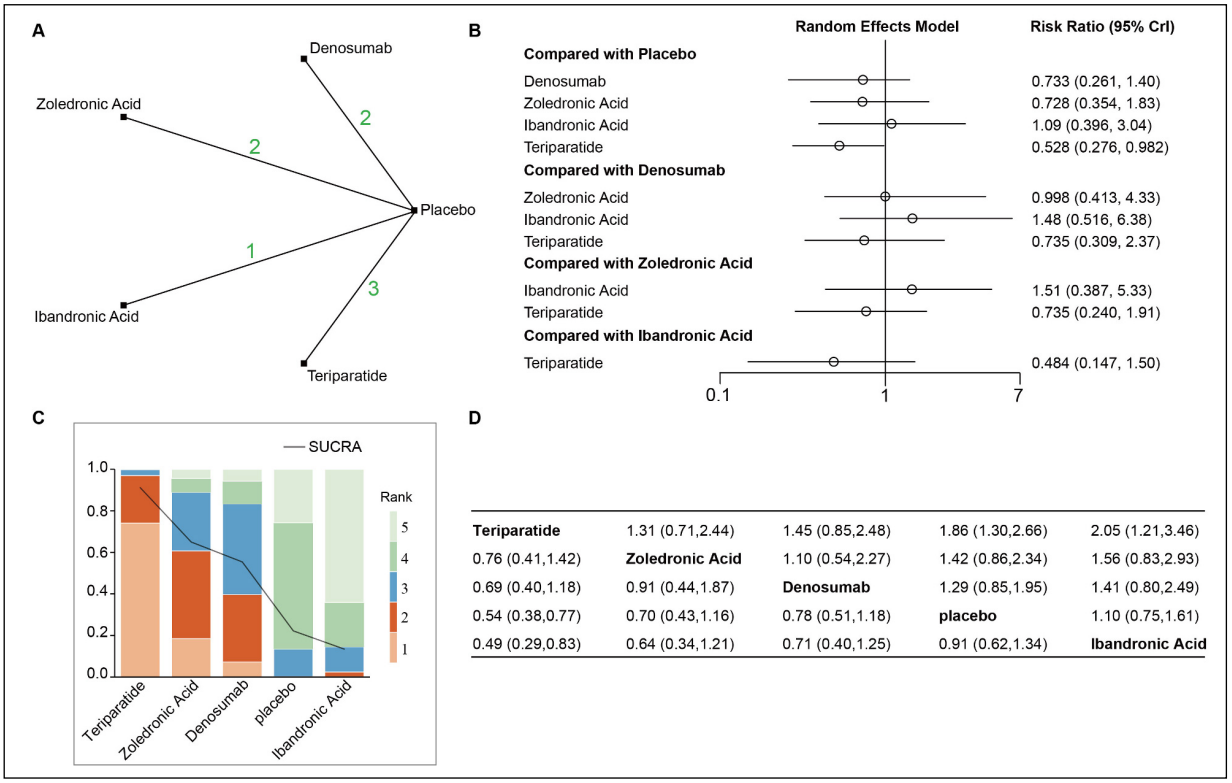

Figure 4. Summary of network meta-analysis of non-vertebral fracture outcomes. **A**, The network plots. **B**, Forest map of network comparison. **C**, Cumulative probability rank. **D**, Net-league table.

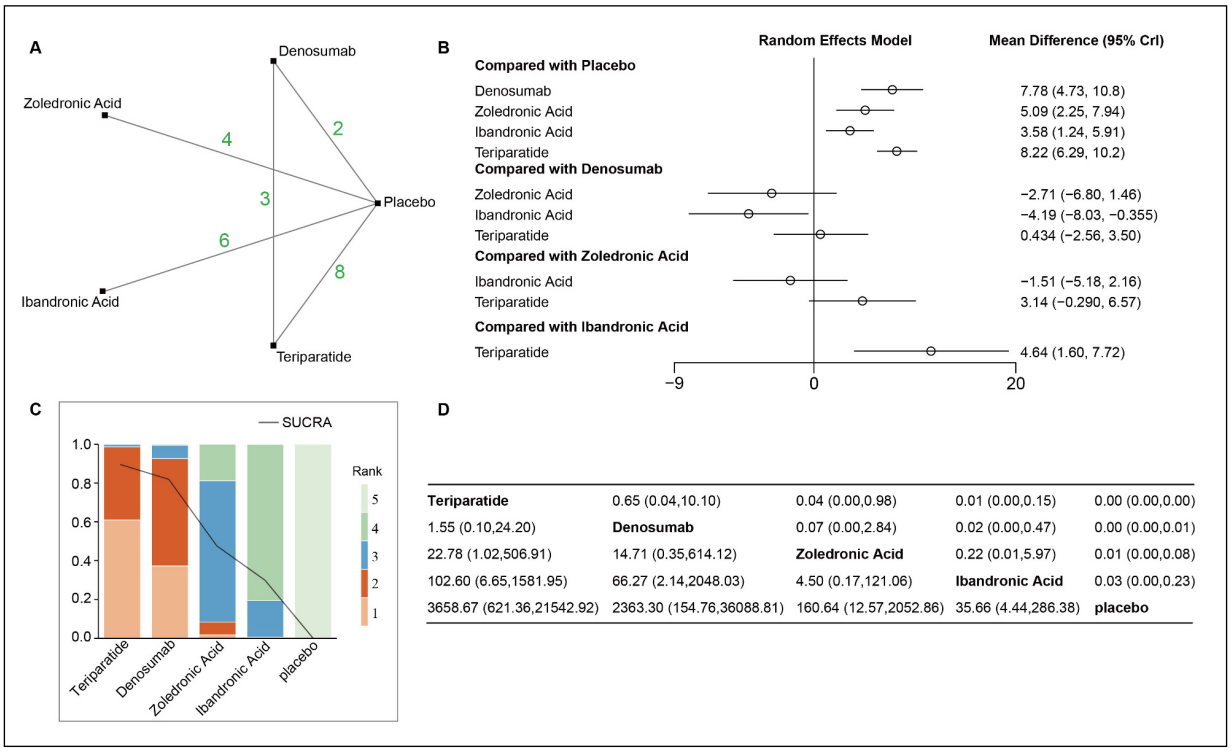

Figure 5. Summary of network meta-analysis of Spine BMD outcomes. **A**, The network plots. **B**, Forest map of network comparison. **C**, Cumulative probability rank. **D**, Net-league table.

Femoral Neck BMD

Seventeen[16,23,24,29,32,39,41,42,43,48,49,50,56,58,65,68,69] RCTs reported the effects of the four drugs on femoral neck BMD. Denosumab [MD = 4.64; 95% CI (2.49, 6.67)] and teriparatide [MD = 3.12; 95% CI (1.38, 4.87)] significantly increased femoral neck BMD compared to placebo. The ranking based on SUCRA values for femoral neck BMD was as follows: denosumab (SUCRA = 0.971) > teriparatide (SUCRA = 0.698) > zoledronic acid (SUCRA = 0.417) > ibandronic acid (SUCRA = 0.36) > placebo (SUCRA = 0.053) (**Supplementary Figure 5**).

One-Third Radius BMD and Radius BMD

One-third radius BMD and radius BMD were reported in 4[29,50,69,70] and 5[39,42,43,48,58] RCTs, respectively. Denosumab was superior to teriparatide in increasing one-third radius BMD [MD = -3.63; 95% CI (-7.04, -0.151)] and radius BMD [MD = -4.14; 95% CI (-6.72, -1.54)]. The ranking based on SUCRA values was denosumab (SUCRA = 0.994) > placebo (SUCRA = 0.464) > teriparatide (SUCRA = 0.043) for one-third radius BMD, and denosumab (SUCRA = 0.999) > zoledronic acid (SUCRA = 0.668) > teriparatide (SUCRA = 0.294) > placebo (SUCRA = 0.004) for radius BMD (**Supplementary Figures 6** and **Supplementary Figures 7**).

Safety

We analyzed three outcomes to evaluate safety: the primary safety outcome were adverse events, the secondary outcomes were serious adverse events and drug-related adverse events. Teriparatide showed a better safety profile compared to other drugs in terms of adverse events. The results for safety-related outcomes were similar between placebo and the four osteoporosis treatments.

Adverse Events

Adverse events were evaluated in 30[15-17,25-27,29-31,33,36,37,40,41,44,48-57,59,61-63,65] RCTs, including four types of anti-osteoporosis drugs (denosumab *vs.* placebo, n = 7[17,29,40,44,50,52,57]; zoledronic acid *vs.* placebo, n = 6[26,27,31,48,59,63]; ibandronic acid *vs.* placebo, n = 7[16,25,33,49,53,61,62]; teriparatide *vs.* placebo, n = 9[30,36,37,41,51,54-56,65]; zoledronic acid *vs.* teriparatide, n = 1[15]). As shown in Figure 6, only zoledronic acid significantly increased the risk of adverse events [RR = 1.03; 95% CI (1.01, 1.06)] compared

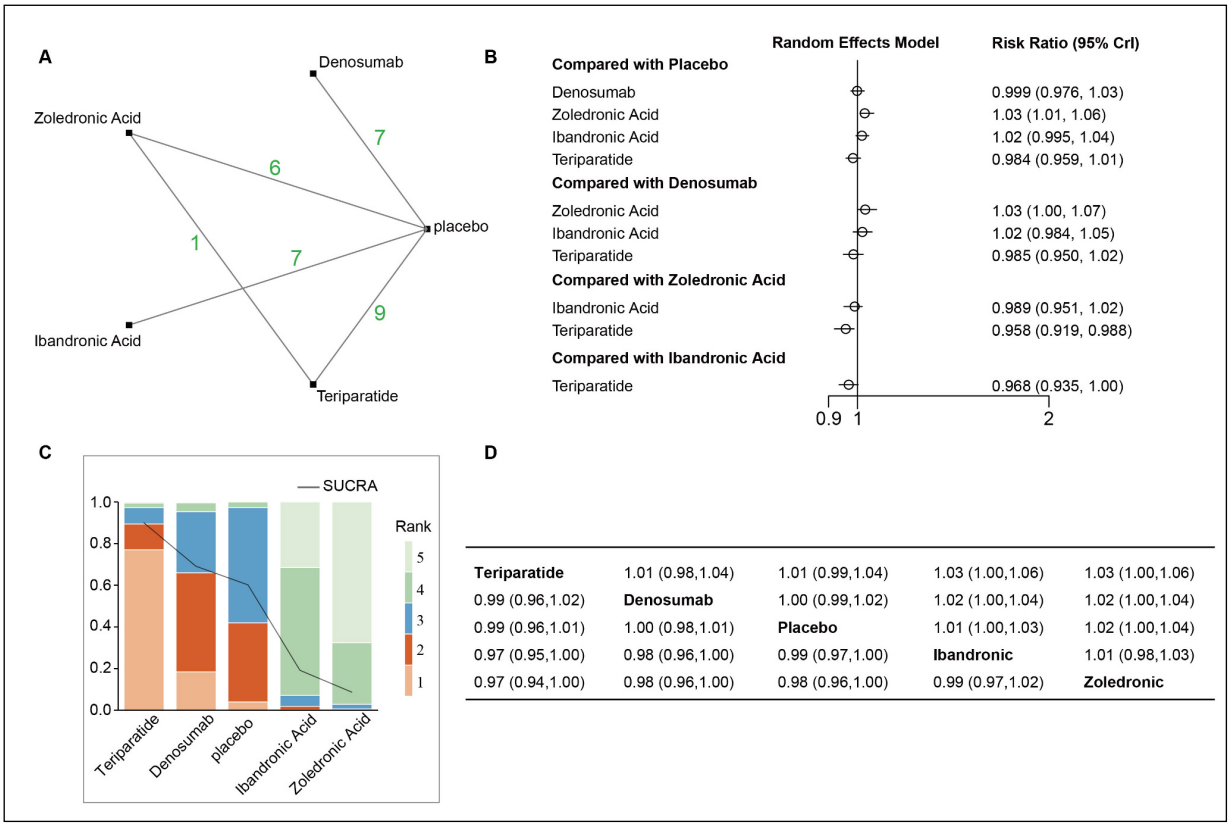

Figure 6. Summary of network meta-analysis of Adverse events outcomes. **A**, The network plots. **B**, Forest map of network comparison. **C**, Cumulative probability rank. **D**, Net-league table.

to placebo. Moreover, the risk of adverse events was significantly lower in the teriparatide group [RR = 0.958; 95% CI (0.919, 0.988)] compared to the zoledronic acid group. The ranking based on SUCRA values for adverse events was as follows: teriparatide (SUCRA = 0.908) > denosumab (SUCRA = 0.698) > placebo (SUCRA = 0.608) > ibandronic acid (SUCRA = 0.195) > zoledronic acid (SUCRA = 0.09).

Serious Adverse Events

Serious adverse events were analyzed in 23[17,23,26,27,29,33,35,37,40,41,44,48,49,50,51,53,54,57,59,61-63,66] RCTs (denosumab *vs.* placebo n = 6[17,29,40,44,50,57]; zoledronic acid *vs.* placebo n = 6[23,26,27,48,59,63]; ibandronic acid *vs.* placebo n = 6[33,49,53,61,62,66,]; teriparatide *vs.* placebo n = 4[37,41,51,54]; zoledronic acid *vs.* teriparatide n = 1[35]). There was no significant difference in serious adverse events among the four anti-osteoporosis drugs. The ranking based on SUCRA values for serious adverse events was as follows: teriparatide (SUCRA = 0.813) > zoledronic acid (SUCRA = 0.612) > placebo (SUCRA = 0.468) > ibandronic acid (SUCRA = 0.408) > denosumab (SUCRA = 0.199) (**Supplementary Figure 8**).

Drug-Related Adverse Events

Drug-related adverse events were reported in 9[16,29,33,37,40,41,53,62,67] RCTs (denosumab *vs.* placebo n = 2[29,40]; ibandronic acid *vs.* placebo n = 5[16,33,53,62,67]; teriparatide *vs.* placebo n = 2[37,41,]). There was no significant difference in drug-related adverse events among the three anti-osteoporosis drugs. The ranking based on SUCRA values was as follows: placebo (SUCRA = 0.696) > teriparatide (SUCRA = 0.688) > ibandronic acid (SUCRA = 0.353) > denosumab (SUCRA = 0.263) (**Supplementary Figure 9**).

Cluster Rank for Safety and Efficacy

Based on the cluster rank analysis (Figure 7A), teriparatide (70.9, 90.8) and denosumab (80.6, 69.8) were associated with reduced incidence of both adverse events and vertebral fractures compared to placebo (0.5, 60.8), ibandronic acid (25.7, 19.5), and zoledronic acid (72.3, 9). The cluster rank for adverse events and spine BMD showed similar results (Figure 7B).

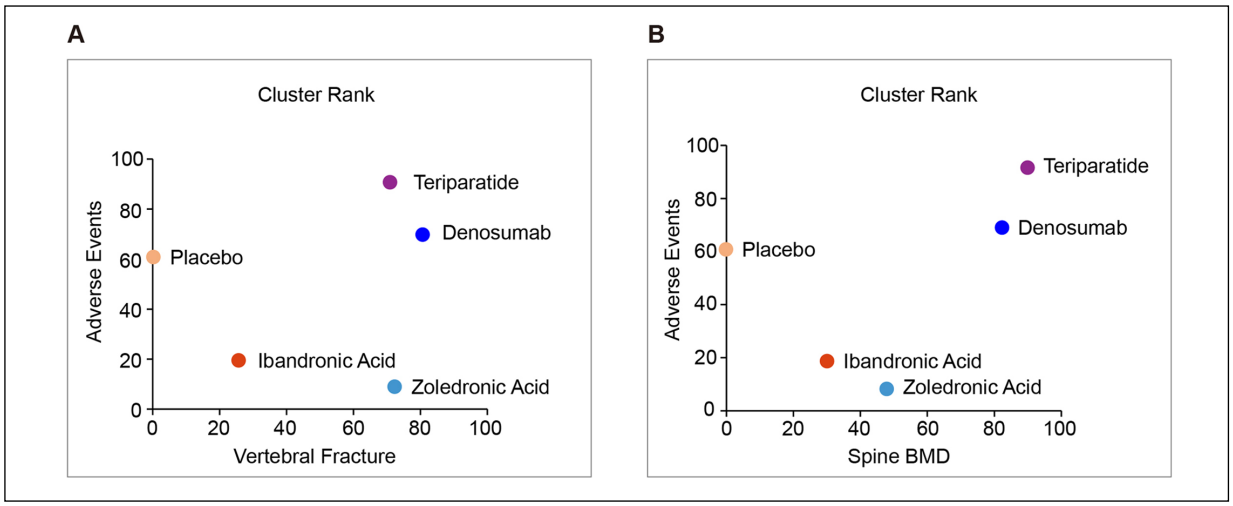

Figure 7. **A**, The cluster rank of adverse events and vertebral fracture. **B**, The cluster rank of adverse events and spine BMD.

Discussion

Postmenopausal osteoporosis is closely associated with fractures, which can significantly increase frailty, life limitation, living dependency, and even mortality[1]. This network meta-analysis was conducted to evaluate the efficacy and safety of denosumab, teriparatide, zoledronic acid, and ibandronic acid in women with postmenopausal osteoporosis. Through a systematic search, we included 51 RCTs with a total of 39,095 patients and evaluated the effect of these four drugs on the ten outcomes, including vertebral fracture, non-vertebral fracture, spine BMD, total hip BMD, femoral neck BMD, one-third radius BMD, radius BMD, adverse events, serious adverse events, and drug-related adverse events. As the SUCRA values indicated, denosumab was the best choice to improve radius BMD, hip BMD, femoral neck BMD, one-third radius BMD, and reduce vertebral fracture. Besides, teriparatide was the best choice to prevent adverse events, serious adverse events, non-vertebral fractures, and improve spine BMD. Moreover, placebo performed best in preventing drug-related adverse events. Therefore, denosumab and teriparatide might be a better choice for women with postmenopausal osteoporosis.

Efficacy assessment of anti-osteoporosis drugs is crucial in clinical therapy. The effectiveness of teriparatide for women with postmenopausal osteoporosis remains a topic of controversy. Several RCTs[65,89,90] have shown a decrease in total hip BMD after teriparatide treatment. However, Body et al[89] report that teriparatide increased lumbar spine BMD and total hip BMD by increasing bone Alkaline phosphatase (ALP) and N-telopeptide of type I collagen (NTX) levels in women with postmenopausal osteoporosis. In addition, consistent with our findings, a meta-analysis[92] supported a significant improvement in lumbar bone density with teriparatide. Unlike other antiresorptive medications, long-term denosumab treatment is accompanied by a continuous increase in BMD. Zhang's meta-analysis has demonstrated the potential superiority of denosumab against other drugs (including teriparatide)[93]. A network meta-analysis by Migliorini et al[94] also showed that denosumab contributed to increased BMD in the spine, with the greatest impact on hip and femur BMD. Our study confirmed and expanded upon previous research, suggesting that among the four drugs investigated, denosumab was more effective than teriparatide, and teriparatide was better than ibandronic acid in improving spine BMD, which implied that denosumab may be the optimal choice for improving spine BMD. However, it is important to note that there was heterogeneity, and the sample size was small (vertebral fracture, n = 1; spine BMD, n = 2) in the denosumab group. Therefore, further research and clinical data are needed to support the advantage of denosumab in the treatment of postmenopausal osteoporosis.

In clinical treatment, the safety evaluation of anti-osteoporosis drugs is also very important. For instance, Reid et al[95] reported that 78% of patients in the zoledronic acid treatment group experienced adverse events, such as nausea, pyrexia, and back pain. Furthermore, a meta-analysis[96] indicated that the use of zoledronic acid may be associated with an elevated risk of serious atrial fibrillation stroke com-

pared to the control intervention. Similarly, a clinical trial[16] involving ibandronic acid revealed that 75% of patients experienced at least one adverse event in the follow-up period. Among patients receiving denosumab, 95.1% experienced adverse events, most commonly arthralgia, nasopharyngitis, back pain, and so on[29]. In Boonen's study[30,] of patients receiving teriparatide, 83% experienced multiple adverse events, including asthenia, arrhythmia, and hypertension. Several meta-analyses[97] also compared the safety of these four drugs. For example, a meta-analysis indicated that denosumab did not pose a higher risk of serious adverse events[97]. In our study, we carefully assessed adverse events, serious adverse events and drug-related adverse events, and the results showed there was no significant difference in the occurrence of both the serious adverse events and drug-related adverse events, while zoledronic acid was associated with a higher risk of adverse events compared to placebo [RR = 1.03; 95% CI (1.01, 1.06)] and teriparatide [RR = 0.989; 95% CI (0.919, 0.988)]. This finding was consistent with Wang's study, which also reported a higher incidence of adverse events in the zoledronic acid group compared to the control group[98]. However, a meta-analysis conducted by Yuan et al[99] demonstrated that teriparatide did not exhibit any superiority in terms of adverse events when compared to bisphosphonates (including zoledronic acid, alendronate, risedronate, and other bisphosphonates). Similar conclusions were reached by Ouyang et al[100]. Additionally, Wu et al[101] found no statistically significant difference in adverse events or withdrawals due to adverse events when comparing denosumab and bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid). However, in our study, we observed that zoledronic acid was associated with a higher incidence of adverse events compared to denosumab [RR = 1.03; 95% CI (1.00, 1.07)]. It is worth noting that the studies by Yuan et al[99] and Wu et al[101]grouped the four different drugs as one group (bisphosphonates). In contrast, our study compared denosumab, ibandronate, and zoledronic acid separately. Ultimately, our study comprehensively evaluated the clinical benefits of these drugs in terms of both efficacy and safety, suggesting that denosumab or teriparatide may be preferable options for patients.

American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis (2020 Update) specified that the effect of the anti-osteoporosis treatment can be monitored by serial changes in lumbar spine, total hip, or femoral neck BMD (Grade B; BEL 1, downgraded due to limited evidence). According to the guidelines, stable or increasing BMD, with no evidence of new fracture or vertebral fracture progression were considered as a positive response to therapy for osteoporosis (Grade A; BEL 1)[102]. The clinical administration plan for osteoporosis is influenced by various factors. In most cases, oral bisphosphonates, such as ibandronic acid, are the preferred initial choice. However, denosumab can be an alternative for women who are intolerant to bisphosphonates[10]. It's important to note that treatment with denosumab is reversible, and discontinuation can lead to a rapid increase in bone turnover and subsequent bone loss. This increases the risk of fracture, making lifelong use of denosumab necessary. However, patients may discontinue treatment due to side effects. Additionally, treatment with denosumab may increase BMD to a level where continued treatment does not further reduce fracture risk[103]. For people at high risk of fracture, initial treatment with anabolic agents, such as teriparatide, followed by antiresorptive agents like bisphosphonates, is recommended to maintain increased BMD. This sequential therapy may be a clinical strategy for rapid and sustained fracture risk reduction[12]. It's worth mentioning that teriparatide is typically used for a course of 24 months[12,102]. Nowadays, newer anabolic drugs like abaloparatide have been confirmed to have superior therapeutic effects and similar adverse cardiovascular events compared to teriparatide[104]. To date, romosozumab is globally recognized as one of the most effective bone anabolic drugs for anti-osteoporosis treatment. However, it is strictly prohibited for patients who have had a myocardial infarction or stroke within the previous year due to its potential high risk of cardiovascular adverse events[105]. Besides, there is evidence suggesting that medication adherence to anti-osteoporosis agents may be related to fracture risk[106-108]. Keshishian et al[108] illustrated low adherence patients had a 32% and 34% increased risk for hip/pelvis/femur fractures and vertebral fractures, respectively, compared to high adherence patients. Therefore, maintaining a standard administration schedule also appears to be crucial in determining the effectiveness of anti-osteoporosis drugs in real-life clinical practice.

Limitations

We acknowledge several limitations in our study. Firstly, there were variations in drug administration routes and doses among the included studies, which may have influenced the efficacy outcomes. For example, some subjects in

the ibandronic acid group received the drug *via* intravenous injection, while others used the oral administration method. Secondly, the follow-up periods varied across the included studies, which could have affected the reliability of the outcomes. Thirdly, while most of the included studies permitted patients to take daily calcium and/or vitamin D supplements, a few studies did not provide information on whether subjects received supplementation. Additionally, there were no restrictions on the countries where the clinical trials were conducted. Lastly, some studies used teriparatide as a positive control in open-label designs, which may have introduced bias into our analysis.

Conclusions

Our study demonstrated that teriparatide significantly decreased the occurrence of vertebral fractures when compared to ibandronic acid. Additionally, both denosumab and teriparatide were found to significantly enhance spine BMD compared to ibandronic acid. Furthermore, denosumab exhibited significant improvements in radial BMD, hip BMD, and one-third radius BMD compared to teriparatide. Lastly, teriparatide showed a significant decrease in the risk of adverse events compared to zoledronic acid. Therefore, when considering both safety and efficacy, denosumab or teriparatide may emerge as preferred options for women with postmenopausal osteoporosis.

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Ethics Approval and Informed Consent
Not applicable.

Availability of Data and Materials
All the data used in the analysis is sourced from public databases and is presented within the manuscript.

Conflict of Interests
The authors declare no conflict of interest.

Authors' Contributions
Ruxu You designed this study. Wanyu Wang and Linhua Chen screened RCTs, extracted target information and analyzed data. Wanjun Ma and Wanyu Wang wrote this manuscript.

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