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# The effects of teriparatide and bisphosphonates on new fractures in postmenopausal women with osteoporosis

## A protocol for systematic review and meta-analysis

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## Abstract

**Background:** To systematically evaluate the efficacy of teriparatide and bisphosphonates in preventing fractures in postmenopausal women with osteoporosis.

**Materials and methods:** We performed a systematic search of PubMed, Embase, and the Cochrane Library for randomized controlled trials (RCTs) that compared teriparatide and bisphosphonates for osteoporosis treatment. Searches were performed without language restrictions and included studies from beginning of time to March 2019. Two authors independently screened and extracted the selected article. The quality of the included studies was evaluated using the Cochrane system evaluation method. Data were extracted and analysed using RevMan 5.2 software.

**Results:** Nine RCTs were included for a total of 2990 postmenopausal women with osteoporosis. Of these, 1515 patients were treated with teriparatide and 1475 were treated with bisphosphonates. After pooling the data of 9 studies, there were significant differences between teriparatide and bisphosphonates [relative risk (RR): 0.61, 95% confidence interval (CI) (0.51, 0.74)] in the prevention of fractures according to different follow-up durations ($P < .05$), whatever alendronate [RR: 0.51, 95% CI (0.27, 0.95)] and other bisphosphonates [RR: 0.63, 95% CI (0.51, 0.77)]. In addition, we found significant differences between teriparatide and bisphosphonates in the prevention of vertebral fractures [RR: 0.47, 95% CI (0.35, 0.64)] and non-vertebral fractures [RR: 0.76, 95% CI (0.58, 0.99)]. There were no significant differences in adverse effects between teriparatide and bisphosphonates [RR: 0.89, 95% CI (0.76, 1.03)].

**Conclusions:** Based on the results of our meta-analysis, teriparatide was better than bisphosphonates in preventing fractures in postmenopausal women with osteoporosis both in the short-term and long-term follow-up periods. Teriparatide was superior to bisphosphonates in preventing vertebral and non-vertebral fractures. These drugs did not differ in terms of their adverse effects. More high-quality studies are needed to compare other factors such as costs and adverse reactions.

**Abbreviations:** ALN = alendronate, BMD = bone mineral density, CA = calcium, CI = confidence interval, PBO = placebo, RCT = randomised controlled trial, RIS = risedronate, RR = relative risk, TPTD = teriparatide, VD = vitamin D, ZOL = zoledronate.

**Keywords:** bisphosphonates, fractures, meta-analysis, osteoporosis, postmenopausal woman, teriparatide

## 1. Introduction

Osteoporosis is a common skeletal disease that is characterised by bone loss, increased bone fragility, and bone structure destruction.[1,2] There are approximately 200 million patients with osteoporosis, and more than 8.9 million fractures worldwide are attributed to osteoporosis each year.[3] In the United States and

Europe, about 30% of all postmenopausal women have osteoporosis.[4] Postmenopausal women are one of the main risk groups for osteoporosis. Postmenopausal women have decreased oestrogen levels, leading to more bone resorption and less bone formation, unbalanced bone remodelling, and loss of bone mass. Ultimately, these conditions lead to the development of postmenopausal osteoporosis, which increases the risk of fractures.[5] Therefore, the aim of osteoporosis treatment is to improve bone strength and reduce the risk of fractures by increasing bone mass or reducing bone resorption.

Currently, approved anti-osteoporosis medications are classified as either anti-resorptive drugs or anabolic drugs. Although there are several anti-resorptive drugs and anabolic drugs currently in use, the main anti-resorptive drug is bisphosphonates, which are typically the first-line anti-osteoporosis medication.[6,7] Some examples of bisphosphonates are risedronate, zoledronate (ZOL), and alendronate. These drugs are inexpensive, convenient, and widely used in various types of osteoporosis. By contrast, the main anabolic drug is the N-terminal fragment teriparatide (PTH 1-34).[8,9] Although the 2 types of anti-osteoporosis drugs have different mechanisms of action, they have similar indications and have shown beneficial effects in treating osteoporosis in postmenopausal women.

Currently, several randomized controlled trials (RCTs) and meta-analyses have compared the safety and efficacy of bisphosphonates and teriparatide in postmenopausal osteoporosis.[10–12] In these studies, bone mineral density (BMD) was the main study outcome evaluation index.[13,14] Many studies have indicated that teriparatide increases BMD better than bisphosphonates in postmenopausal women with osteoporosis. However, fracture is a serious complication of osteoporosis, and few meta-analysis study had compared the effects of teriparatide and bisphosphonates using reduced incidence of fractures as the main outcome. Indeed, the majority of meta-analyses did not use fracture as a primary outcome. Consequently, they only included studies that reported on the primary outcome of their research and excluded studies on fractures that did not include that outcome. In addition, some meta-analyses compared drugs with placebo (PBO), rather than directly comparing the effects of teriparatide and bisphosphonates in RCTs. Diez-Perez described the effects of teriparatide on the incidence of new fractures, the effects of teriparatide were compared to other drugs, not to bisphosphonates alone.[15] Fei Yun[16] compared teriparatide and bisphosphonates through meta-analysis. But there are 2 studies[17,18] with duplicate data in Fei Yun study. Recently, Kendler et al[18] reported that prior to the VERO trial no comparative trials between teriparatide and bisphosphonates with fracture as the endpoint had been performed. The authors compared teriparatide with risedronate in the treatment of 1360 postmenopausal women with osteoporosis, and fracture was the primary outcome observed in their study. Their RCT was included in our current study. The goal of our study was to describe in detail the independent effects of bisphosphonate and teriparatide on new fractures

The purpose of this study was to understand the effectiveness of bisphosphonates and teriparatide in reducing the incidence of fractures in postmenopausal women with osteoporosis. RCTs that used fracture as an outcome were collected for this meta-analysis. And the RCT included was a head-to-head study of the 2 drugs. Results from this study may provide insight in choosing medications.

## 2. Materials and methods

### 2.1. Search strategy

Shuilin Chen and Yulong Ouyang performed a systematic search of PubMed, the Cochrane Library, and Embase databases. We retrieved studies that compared teriparatide and bisphosphonates in the treatment of postmenopausal osteoporosis, from beginning of time to March 2019. We also traced the references cited in the selected articles. The following keywords were used in the search: osteoporosis, postmenopausal, teriparatide, parathyroid, risedronate, ZOL, bisphosphonates, alendronate, and phosphoric acid.

### 2.2. Inclusion and exclusion criteria for the studies

The studies were selected according to the following inclusion criteria:

1. RCT comparing teriparatide and bisphosphonate in the treatment of osteoporosis;
2. RCT in which the study subjects were postmenopausal women with osteoporosis or osteopenia; and
3. RCT involving a treatment duration of at least 6 months.

The exclusion criteria were

1. clinical studies with a design other than an RCT (e.g., retrospective clinical trials, non-randomised controlled studies, and observational studies);
2. abstracts with no full-text reports;
3. repeated publications and incomplete information;
4. conference reports;
5. retrospective studies and meta-analyses;
6. no information on the number of adverse fracture events or the incidence of adverse fracture events; and
7. fewer than 30 cases studied.

### 2.3. Data extraction and analysis index

The selected articles were independently screened and extracted by 2 researchers. Discrepancies in data extraction were discussed with Ting Wan until a consensus was reached. All data were independently cross-checked by 2 authors. We omitted the author names, publication name, year, and country from the extracted data to avoid subjective bias. The extracted data included basic characteristics of patients, intervention measures, number of new vertebral or non-vertebral fractures, follow-up duration, and number of adverse effects. We defined both new and worsened fractures as new fractures. All studies were entered into the meta-analysis, and subgroup analyses according to types of medication, fracture site, median age, and follow-up time were performed.

### 2.4. Quality assessment

We used the Cochrane risk of bias tool to assess the quality of the selected studies, including whether the randomisation was performed correctly, whether random allocation was concealed, whether the blinding method was applied, whether intention-to-treat analysis was used in the processing of results, and the integrity of follow-up. Each category was categorised by 3 levels: low risk, ambiguous risk, and high risk.

## 2.5. Statistical analysis

Yulong Ouyang performed the statistical analysis. We used RevMan software (RevMan version 5.2; The Cochrane Collaboration, Copenhagen, Denmark) for meta-analysis. The weights of each study will be calculated by RevMan and the blue squares in the forest map represent different weights for each study. RR was used as the effect quantity. The clinical heterogeneity of the included studies was tested (Q test). If there was insignificant heterogeneity among the studies ($P > .05$, $I^2 < 50\%$), we used a fixed-effects model for meta-analysis. On the contrary, if heterogeneity existed among the studies ($P < .05$, $I^2 > 50\%$), we used a random-effects model for analysis. Subgroup analysis of factors that may lead to heterogeneity was used for qualitative reasons.

## 3. Results

### 3.1. Literature search

A total of were acquired from searching the 3 databases (230 in PubMed, 57 in Cochrane Library, and 437 in Embase). From these, we excluded 178 records because of duplicate publications, reading topics, and abstracts. Then, we excluded 483 studies after reading the abstract. After reading the full-text articles, Ouyang Yulong finally screened out 7 studies, and Shuilin Chen finally screened out 9 studies. Seven of those are consistent. There are some discrepancies result in 2 researcher. Because 2 studies reported that the incidence of fractures was zero in each group. After discussion with Ting Wan, the same 7 studies met the criteria and we think that even if the fracture rate is zero, it should be included. Finally, 9 RCTs were included in our meta-analysis.[18–26] A total of 2990 menopausal women with osteoporosis were included in the RCTs. Of the 9 RCTs, 5 investigated alendronate versus teriparatide,[21–25] 3 investigated risedronate versus teriparatide,[18–20] and 1 investigated zoledronic acid vs teriparatide.[26] A flow diagram of the number of records at each stage can be seen in Figure 1.

### 3.2. Patient characteristics

The baseline characteristics of the patients and the types of drug interventions used are shown in Table 1. In each study, all patients received supplementation with 500 to 1250 mg calcium and 400 to 1200 IU vitamin D (VD) (orally, daily). Each study was compared for different types and doses of bisphosphonates
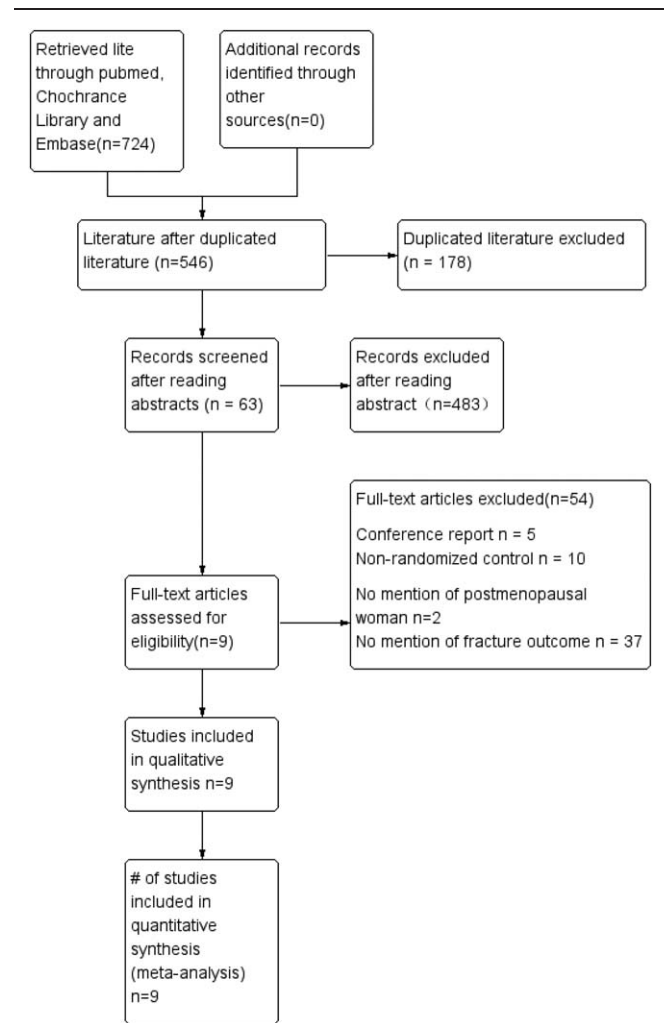


**Figure 1.** Flow diagram.

medications. The follow-up time ranged from 12 to 24 months. The specific drugs and drug doses of each study were shown in Table 1.

The 9 eligible studies included 2990 participants. In these studies, there were 176 cases of vertebral fractures and 200 cases of non-vertebral fractures. The teriparatide group included 1515

**Table 1**

**General characteristics of the included studies.**

| Study ID | Number of patients (TPTD/BP) | Age, years | | Intervention | | | Interventional time, months |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | TPTD | BP | TPTD | BP | Additional treatment | |
| BODY (2002) | 146 (73/73) | 65 ± 9 | 66 ± 8 | TPTD (40 μg/d)+PBO (10 mg/d) | PBO (40g/d)+ALN (10 mg/d) | CA (1000 mg/d)+VD (400–1200 IU/d) | 12 |
| McClung (2005) | 203 (102/101) | 65.3 ± 8.4 | 67.1 ± 5.8 | TPTD (20 μg/d)+PBO (10 mg/d) | PBO (20 μg/)+ALN (70 mg/w) | CA (1000mg/d)+VD (400–800 IU/d) | 18 |
| McClung (2014) | 106 (55/51) | 66.8 ± 5.7 | 62.1 ± 1.2 | TPTD (20 μg/d) | ALN (10 mg/day) | CA (1,000 mg/d)+VD (800 IU/d) | 12 |
| Jing Deng (2018) | 65 (43/22) | 62.88 ± 5.80 | 62.77 ± 6.42 | TPTD (20 μg/d) | ALN (70 mg/w) | CA (1250mg/d)+VD (200IU/d) | 12 |
| Annalisa Panico (2011) | 81 (42/39) | 65 ± 9 | 60 ± 14.4 | TPTD (20 μg/d) | ALN (70 mg/w) | CA (1,000mg/d)+VD (800 IU/d) | 18 |
| Hadji (2011) | 710 (360/350) | 70.5 ± 8.8 | 71.6 ± 8.1 | TPTD (20 μg/d)+PBO (35 mg/w) | PBO (20 μg/d)+RIS po (35 mg/w) | CA (1,000 mg/d)+VD (800 IU/d) | 18 |
| David L Kendler (2018) | 1360 (680/680) | 72.6 ± 8.77 | 71.6 ± 8.58 | TPTD (20 μg/d)+PBO po (35 mg/w) | PBO (20 μg/)+RIS (35 mg/w) | CA (500–1000mg/d) + VD (400–800 IU/) | 24 |
| Cosman (2011) | 275 (138/137) | 63.8 ± 9.1 | 66.1 ± 9.0 | PBO IV+TPTD (20 μg/d) | ZOL IV (5/day) | CA (1000–1200mg/d)+VD (400–800 IU/d) | 12 |
| Anastasilakis(2008) | 44 (22/22) | 65.4 ± 1.6 | 64.7 ± 1.5 | TPTD (20 μg/d) | RIS (35 mg/w) | CA (500mg/d)+VD (400IU/d) | 12 |

* Administration model: TPTD subcutaneous injection; ALN, RIS, CA and VD oral; PBO: oral or subcutaneous injection.

Fracture distribution tables.

| Study ID | Vertebral fracture | | Non-vertebral fracture (Hip fracture) | | Incidence of fracture | | Sample size | |
|---|---|---|---|---|---|---|---|---|
| | TPTD | BP | TPTD | BP | TPTD | BP | TPTD | BP |
| Panico (2011) | 1 | 6 | 40 (0) | 0 (0) | 1 | 6 | 42 | 39 |
| BODY (2002) | 0 | 0 | 3 (0) | 10 (0) | 3 | 10 | 73 | 73 |
| Cosman (2018) | 1 | 5 | 7 (0) | 8 (0) | 8 | 13 | 138 | 137 |
| Kendler (2018) | 31 | 69 | 40 (2) | 57 (6) | 71 | 126 | 680 | 680 |
| Hadji (2011) | 24 | 39 | 28 (5) | 29 (2) | 52 | 68 | 360 | 350 |
| Deng (2018) | 0 | 0 | 0 (0) | 1 (0) | 0 | 1 | 43 | 22 |
| Anastasilakis (2008) | 0 | 0 | 0 (0) | 0 (0) | 0 | 0 | 22 | 22 |
| McClung (2005) | 0 | 0 | 9 (0) | 8 (0) | 9 | 8 | 102 | 101 |
| McClung (2014) | 0 | 0 | 0 (0) | 0 (0) | 0 | 0 | 55 | 51 |
| Total | 57 | 119 | 87 | 113 | 144 | 232 | 1515 | 1475 |

patients, of whom 144 had fractures. This was subdivided into 57 vertebral fractures and 87 non-vertebral fractures, of which 7 were hip fractures. The bisphosphonates group included 1475 patients, of whom 232 had fractures. This was subdivided into 119 vertebral fractures and 113 non-vertebral fractures, of which 8 were hip fractures, as shown in Table 2.

There were 931 adverse effects in teriparatide and 961 adverse effects of bisphosphonates were shown in Table 3.

### 3.3. Quality of trials

All RCTs had a low risk of bias in the categories of outcome evaluation and selective publication. Two studies had a high risk of bias in the integrity of outcome data, because of the high rate of loss to follow-up and the inconsistent proportion of reasons for missing participants. None of the other studies had a high risk in any aspect of evaluation. The risk bias assessment is shown in Figure 2.

### 3.4. Meta-analysis

A total of 9 studies reported the number of fractures after treatment with the 2 drugs. However, 2 studies reported that the incidence of fractures was zero in each group. After excluding these studies, the result of meta-analysis is the same as those of including the 2 studies and there is no influence on the results of meta-analysis. We included 7 studies for meta-analysis that not only had no impact on the results, but also had better forest plots. So, we included 7 studies in analyzing fracture incidence, and 9 studies in analyzing adverse effects.

### 3.5. Incidence of fractures and subgroup analysis by medication

Seven RCTs reported the number of fractures following treatment with bisphosphonates or teriparatide (Fig. 3). There were significant differences in the incidence of fractures between postmenopausal patients with osteoporosis who were treated with teriparatide and those treated with bisphosphonates [RR: 0.61, 95% CI (0.51, 0.74), $P < .00001$]; outcomes were significantly better in the teriparatide group than in the bisphosphonate group. There was no significant heterogeneity between trials ($P = .33$, $I^2 = 13\%$).

Analysis of subgroups stratified by medication type indicated that there were significant differences between teriparatide and alendronate. Teriparatide was better than alendronate in preventing fractures in postmenopausal women with osteoporosis [RR: 0.51, 95% CI (0.27, 0.95), $P = .03$]. And teriparatide was superior to other bisphosphonate in preventing fractures in postmenopausal women with osteoporosis [RR: 0.63, 95% CI (0.51, 0.77), $P < .0001$]. There was no evidence of significant heterogeneity between each subgroup ($P > .05$, $I^2 < 50\%$) (Fig. 3).

### 3.6. Incidence of vertebral fractures and subgroup analysis

The effects of teriparatide and bisphosphonates in preventing vertebral fractures were compared and are shown in Figure 4. All studies showed no significant differences in the heterogeneity test ($I^2 = 0\%$, $P = .44$); however, there were statistically significant

Tables of adverse effects.

| Study ID | TPTD | | BP | |
|---|---|---|---|---|
| | Adverse effects | Sample size | Adverse effects | Sample size |
| Annalisa Panico (2011) | 12 | 42 | 14 | 39 |
| BODY (2002) | 10 | 73 | 14 | 73 |
| Cosman (2018) | 7 | 138 | 6 | 137 |
| David L Kendler (2018) | 495 | 680 | 500 | 680 |
| Hadji (2011) | 285 | 360 | 285 | 350 |
| Jing Deng (2018) | 25 | 43 | 6 | 22 |
| Anastasilakis (2008) | 11 | 22 | 7 | 22 |
| McClung (2005) | 49 | 102 | 85 | 101 |
| McClung (2014) | 37 | 55 | 44 | 51 |
| Total | 931 | 1515 | 961 | 1475 |

Figure 2. Risk bias assessment.

differences between the 2 drugs. These results suggest that teriparatide was better than bisphosphonates in preventing new vertebral fractures [RR: 0.47, 95% CI (0.35, 0.64), $P < .00001$].

### 3.7. Incidence of non-vertebral fractures and subgroup analysis

There were 6 studies that reported the number of new non-vertebral fractures (Fig. 5). There were significant differences between teriparatide and bisphosphonates [RR: 0.76, 95% CI (0.58, 0.99), $P = .04$]. The results showed that teriparatide was superior to bisphosphonates in preventing new non-vertebral fractures. There was no evidence of significant heterogeneity among trials ($P = .47$, $I^2 = 0\%$).

### 3.8. Subgroup analysis by follow-up duration

There were 3 studies with a follow-up duration of 12 months, 3 studies with a follow-up of 18 months, and 1 study with a follow-up of 24 months. There were significant differences between teriparatide and bisphosphonates in studies with a 12-month follow-up [RR: 0.45, 95% CI (0.23, 0.89), $P = .02$]. In studies with a follow-up longer than 18 months, there was no significant heterogeneity ($P = .18$, $I^2 = 39\%$) but teriparatide was still superior to bisphosphonates [RR: 0.63, 95% CI (0.52, 0.78), $P < .0001$] (Fig. 6).

### 3.9. Subgroup analysis by adverse effects

A total of 9 studies reported adverse effects. There was significant heterogeneity between studies ($P < .0001$, $I^2 = 76\%$). Using a random-effects model, we found no significant differences in adverse effects between teriparatide and bisphosphonates in studies [RR: 0.89, 95% CI (0.76, 1.03), $P = .12$] (Fig. 7).

### 3.10. Assessment of study quality

We used funnel charts to assess the publication bias of the included studies. Asymmetry and gaps in the lower right corner of the funnel diagram indicated that the included studies may have a publication bias. Funnel plots of fracture incidence are shown in Figure 8.

## 4. Discussion

It is well known that osteoporosis is a systemic disease and can therefore reduce BMD and induce fractures. In the elderly, fractures can increase the mortality rate, reduce the quality of life, and confer a heavy burden to society and families.[27] There are many drugs that can be used to treat osteoporosis, but most affect either bone resorption or bone synthesis. The most common anti-bone resorption drugs are bisphosphonates, and the most common bone synthesis drug is teriparatide. However, the first observation index in most meta-analyses and systematic reviews is not the number of fractures. This leads to authors omitting studies on the number of fractures during the systematic review screening process. In addition, some systematic reviews did not directly compare teriparatide with bisphosphonates but compared each drug with placebo.

Nine RCTs with a total of 2990 patients were included in this study. A meta-analysis and subgroup analysis was conducted on studies of bisphosphonates and teriparatide, and a detailed evaluation of the incidence of new fractures, vertebral fractures, and non-vertebral fractures was conducted. The meta-analysis suggested the following:

1. in general, teriparatide was better than bisphosphonates in preventing fractures in postmenopausal women with osteoporosis;
2. the subgroup analysis indicated that teriparatide was better than alendronate and other bisphosphonates in reducing the incidence of fractures in postmenopausal women with osteoporosis;
3. for postmenopausal women with osteoporosis, teriparatide was better than all bisphosphonates in preventing vertebral fractures;
4. for postmenopausal women with osteoporosis, the effect of teriparatide was superior to that of bisphosphonates in preventing non-vertebral fractures;
5. according to subgroup analysis by follow-up duration, teriparatide was superior to bisphosphonates regardless of whether it was administered short-term or long-term; and
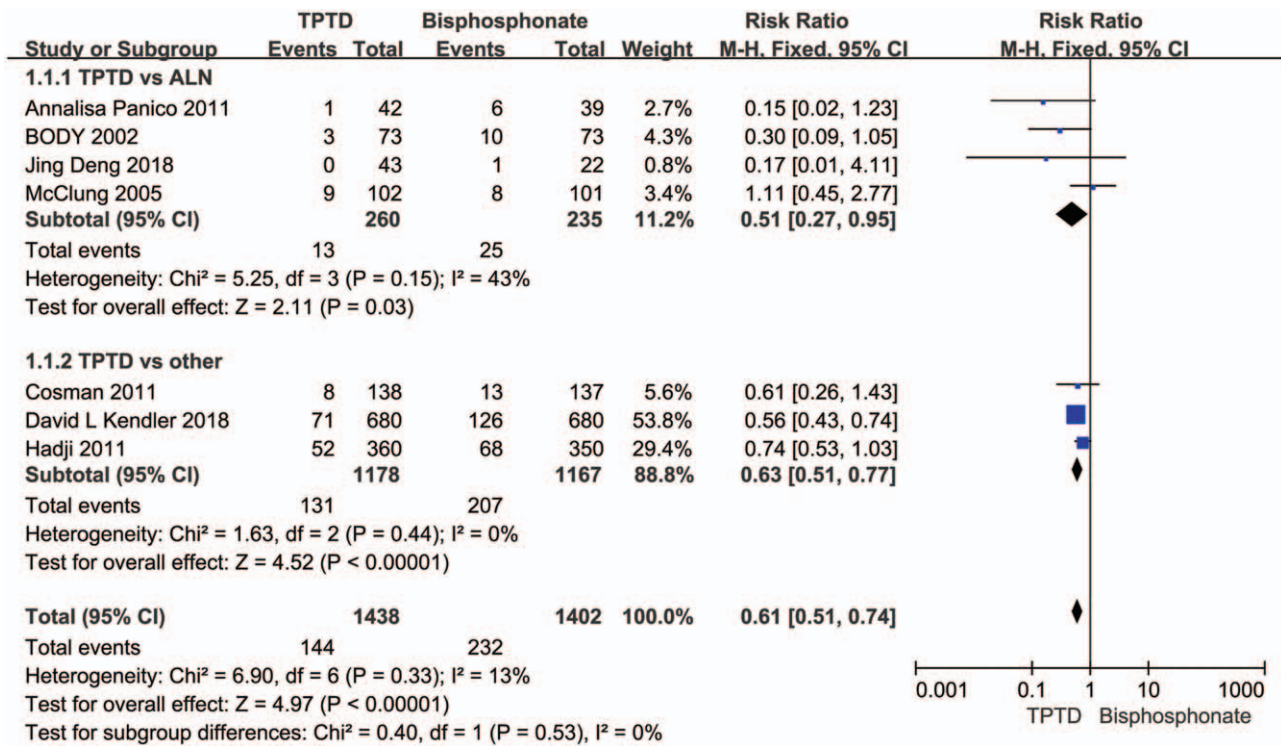
Figure 3. Meta-analysis of the incidence of fractures.

6. according to a subgroup analysis of adverse effects, the safety of teriparatide was similar to bisphosphonates.

At present, whether teriparatide is superior to bisphosphonates is still controversial. Most studies have suggested that teriparatide is more effective than bisphosphonates in improving BMD, especially the BMD of vertebral bones. However, a comparison of these 2 drugs for their ability to prevent new fractures in postmenopausal women with osteoporosis has seldom been reported. With respect to therapeutic efficacy for osteoporosis, Iwamoto et al[28] reported that alendronate and risedronate both had good efficacy in preventing various types of fractures in postmenopausal women with osteoporosis. In addition, a network meta-analysis by Barrionuevo et al[29] showed that teriparatide and most bisphosphonates were effective in preventing fragility. These studies all described the advantages

of using teriparatide and bisphosphonates in postmenopausal women with osteoporosis; however, they did not compare the efficacy of the 2 drugs. Adolfo et al[15] reported teriparatide was significantly better than other controls in preventing hip fracture, and was similar with other controls in humerus, forearm, and wrist fractures. However, this meta-analysis did not perform a direction comparison of teriparatide with bisphosphonates, included both males and females, and included different types of osteoporosis. Our study only observed postmenopausal women with osteoporosis and performed a direct comparison of teriparatide with bisphosphonates. In addition, Wang et al[30] previously showed that teriparatide was superior to alendronate in improving vertebral BMD and preventing fractures in postmenopausal women with osteoporosis. However, this study also showed that the effectiveness of teriparatide in preventing fractures was similar to that of alendronate, independent of
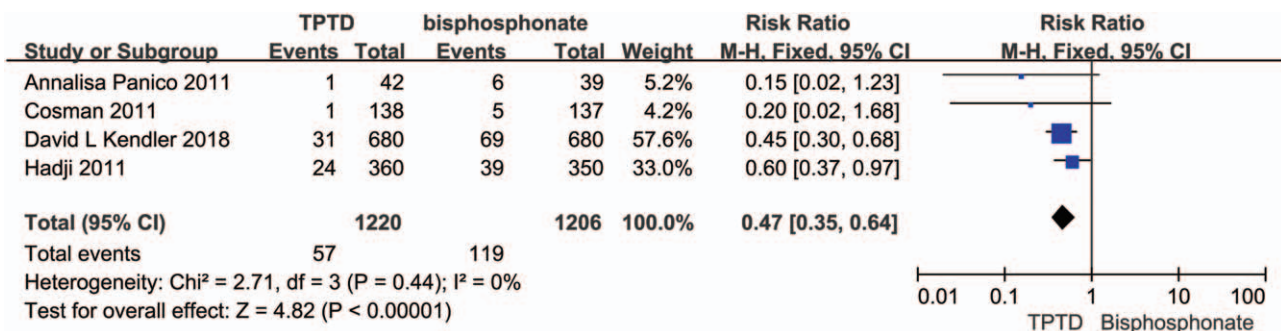


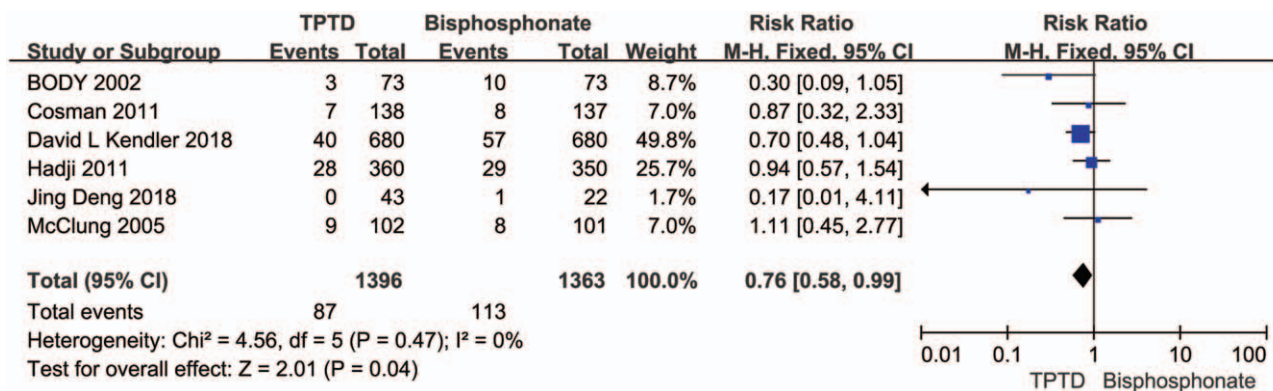Figure 4. Meta-analysis of incidence of vertebral fracture.

**Figure 5.** Meta-analysis of non-vertebral fractures.

whether the fracture was vertebral or non-vertebral. This study considered BMD as the main observation outcome. In addition, this study only included 2 studies with fracture outcomes, and the extracted Body's data[23] on the number of vertebral fractures was incorrect. Body's study did not report the number of vertebral fractures; however, the Wang study extracted such data. Hip fractures are very dangerous for the elderly, as they may lead to serious complications, prolonged bed rest, and eventually death.[31,32] A meta-analysis by Shen et al suggested that there was no significant difference between teriparatide and bisphosphonates in increasing the BMD of the femoral neck, which was similar to our results on hip fracture. However, Shen et al[33] did not describe the incidence of fractures. Albert and Reddy[34] also showed that teriparatide and ibandronate were beneficial in preventing both vertebral and non-vertebral fractures, but that teriparatide had no obvious advantage in reducing hip fractures, as

compared to ibandronate. However, only 2 articles included in our current study described the incidence of hip fracture, which was insufficient for a meta-analysis. Nevertheless, the incidence of hip fracture was the same for both drugs, which suggests that the effect of teriparatide on the prevention of hip fracture was not significantly different from that of bisphosphonates. Therefore, more RCTs comparing teriparatide and bisphosphonates in terms of preventing hip fracture are needed to guide clinical practice.

Many studies reported that teriparatide and bisphosphonates could cause adverse events such as hyperuricemia, back pain, and arthralgia.[35–37] Our study results suggest that teriparatide will not lead to more adverse events than bisphosphonates, and therefore, adverse effects will not limit drug choice. However, a comprehensive understanding of the safety of both drugs requires more studies and classification analyses for different types of adverse events.
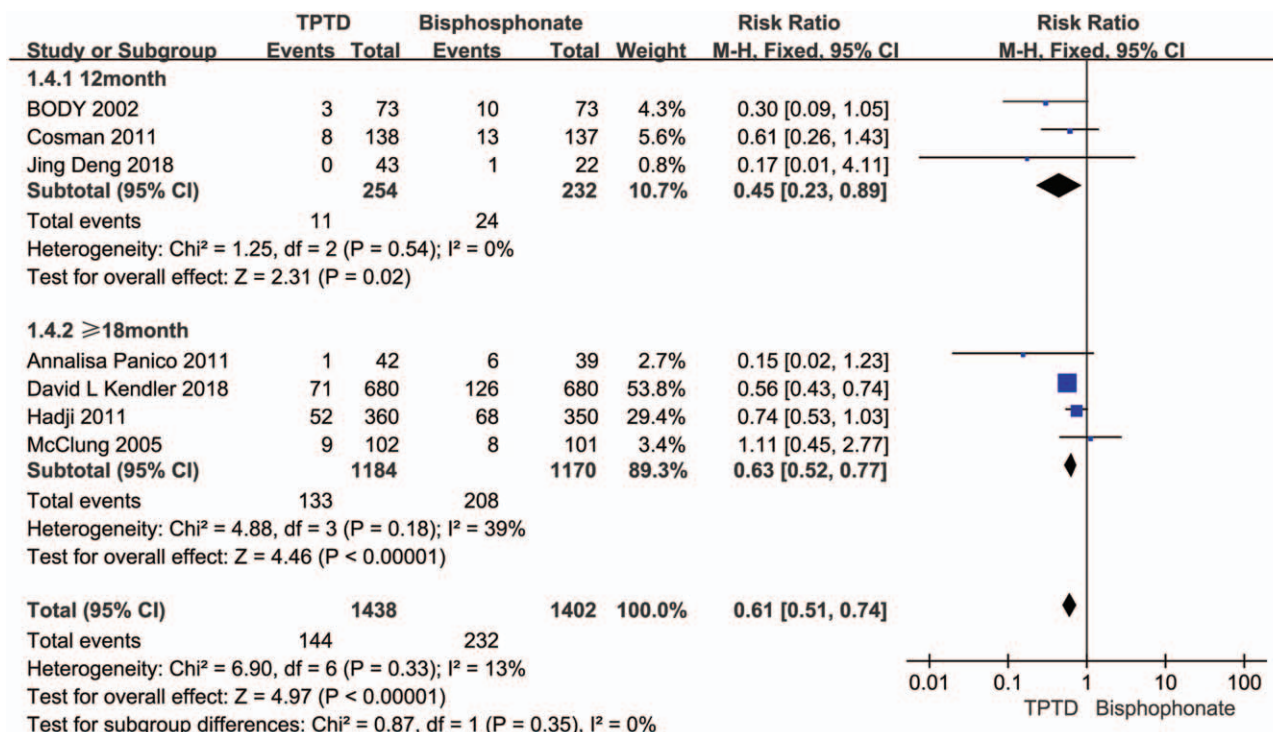


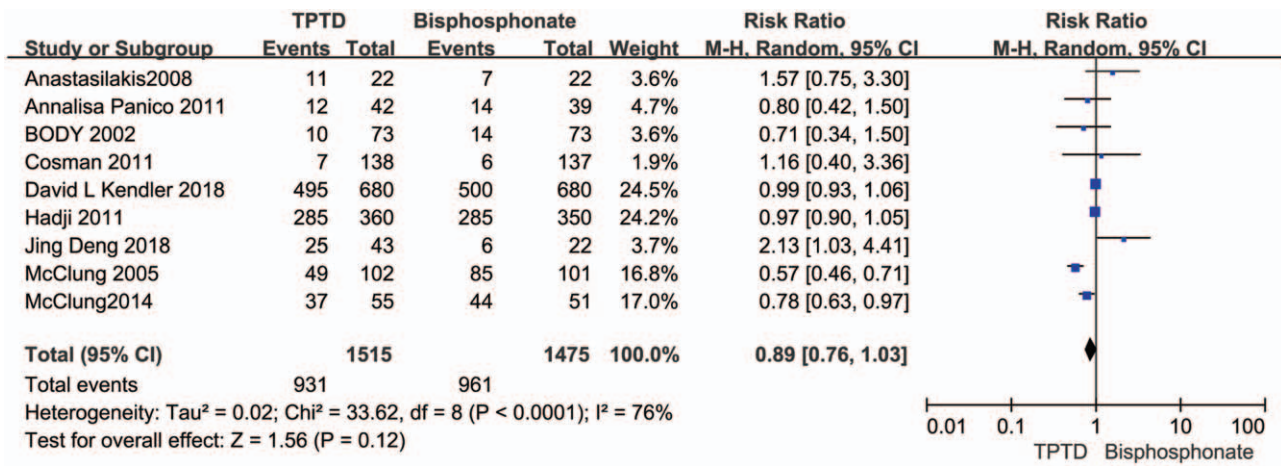**Figure 6.** Meta-analysis of follow-up duration.

**Figure 7.** Meta-analysis of adverse effects.

We can conclude that teriparatide can prevent fracture better than bisphosphonates in clinical medication through our study. It could be a good choice to give priority to teriparatide for postmenopausal women with osteoporosis without considering the economic factors. We hope there will be more head-to-head studies of these 2 drugs with fracture as the main observation index in the future.

### 4.1. Limitations

This study has several limitations:

1. the number of included studies (9) was too small, and may be responsible for the observed publication bias;

2. 2 studies reported "zero" fractures in their analyses. Consequently, they had no effect on fracture outcomes in our meta-analysis, and were used for a meta-analysis of safety, rather than fracture incidence;

3. the funnel plot of the meta-analysis was asymmetric, and the right lower corner was vacant, possibly because small samples with no statistical significance were not reported. However, this possibility was relatively low because most studies suggest that the efficacy of teriparatide is better than that of bisphosphonates. Therefore, if results had shown no statistical significance, the research would likely have been published. The reason for the asymmetry was likely related to the small number of included studies. So, the asymmetry of funnel plot is not affect the conclusions;
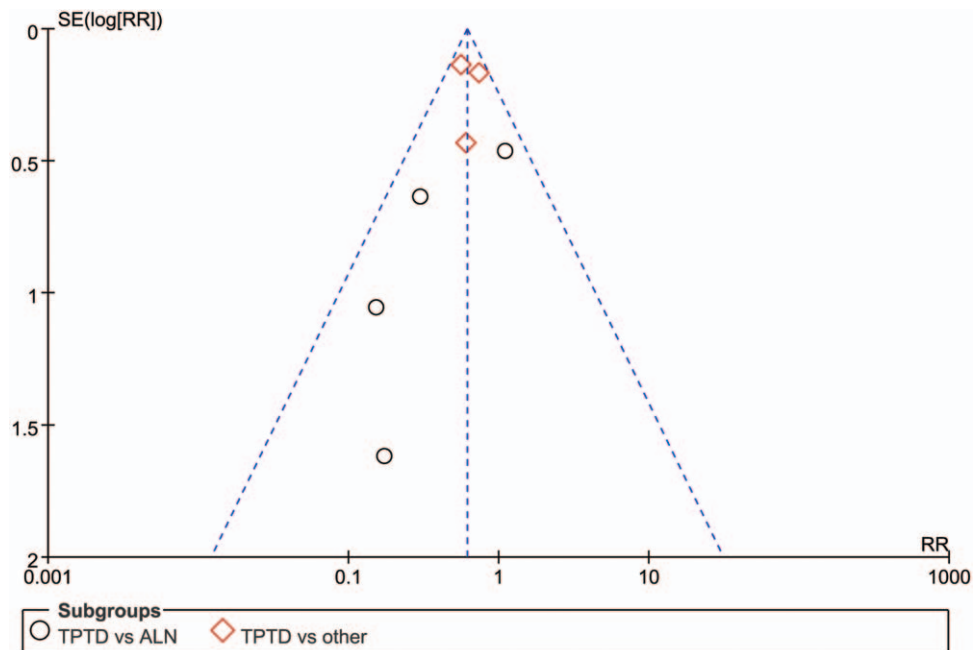


**Figure 8.** Funnel plots of fracture incidence.

4. there were only 2 studies with hip fracture as the outcome, thus preventing a detailed description of this endpoint; and

5. there were differences in the intervention measures and the dosage of calcium and VD supplementation among the studies. Despite these limitations, we hope that this study can provide clinicians with a theoretical basis for clinical medication.

In conclusion, more RCTs that compare the ability of teriparatide and bisphosphonate to prevent fractures in post-menopausal women with osteoporosis are needed to provide a comprehensive assessment that can guide clinical medication.

## 5. Conclusion

According to our meta-analysis, teriparatide was better than bisphosphonates in preventing fractures in postmenopausal women with osteoporosis, both in the short-term and in the long-term. Specifically, teriparatide was superior to bisphosphonates in preventing vertebral fractures and non-vertebral fractures. In terms of adverse effects, both drugs were equally safe. More high-quality studies are needed to compare other factors between these drugs, such as costs and adverse reactions.

## Author contributions

**Data curation:** YuLong Ouyang.
**Formal analysis:** YuLong Ouyang.
**Funding acquisition:** GuiCai Sun.
**Methodology:** GuiCai Sun, ShuiLin Chen.
**Software:** ShuiLin Chen, Ting Wan.
**Visualization:** GuiHao Zheng.
**Writing – original draft:** YuLong Ouyang.
**Writing – review & editing:** GuiCai Sun, ShuiLin Chen.

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