

Effect of bisphosphonate on hip fracture in patients with osteoporosis or osteopenia according to age: a meta-analysis and systematic review

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ABSTRACT

This meta-analysis and systematic review investigated the efficacy of bisphosphonates on the incidence of hip fracture (IHF) in patients of different ages with osteoporosis or osteopenia. We searched Web of Science, Embase, the Cochrane Database, and PubMed from inception to January 10, 2021, for trials reporting the effects of bisphosphonates on the IHF. We included only randomized, double-blind, placebo-controlled clinical trials. We pooled data using a random-effects meta-analysis with risk ratios (RRs) and reported 95% CIs. We also used the Cochran Q and I² statistics to assess the heterogeneity in the results of individual studies. The primary endpoints were the total numbers of people in the bisphosphonates and placebo groups and the numbers of IHFs during the follow-up periods. Bisphosphonates reduced the IHF with an overall effect (RR: 0.66; 95% CI: 0.56 to 0.77; zoledronic acid: RR: 0.60; 95% CI: 0.46 to 0.78; risedronate: RR: 0.74; 95% CI: 0.59 to 0.94, and alendronate: RR: 0.61; 95% CI: 0.40 to 0.95). The result of the heterogeneity assessment was I²=0, p=0.97. In all age groups (all ages, ≥55 years old, ≥65 years old), bisphosphonates reduced the IHF. In the ≥55 years old and ≥65 years old age groups, the RR and 95% CI were 0.63 and 0.43 to 0.93, and 0.60 and 0.44 to 0.81, respectively. Bisphosphonate reduced the IHF in the general population and all age groups (≥55 years old and ≥65 years old). Zoledronic acid, risedronate and alendronate reduced the IHF in osteoporosis or osteopenia populations. The association between bisphosphonate and the IHF does not appear to be influenced by age.

Significance of this study

What is already known about this subject?

- ▶ Bisphosphonates have been used to prevent fracture among populations with osteoporosis.
- ▶ Hip fracture is a serious complication of osteoporosis.
- ▶ The incidence rate of osteoporosis or hip fracture in the elderly is higher than that in the general population.

What are the new findings?

- ▶ Bisphosphonates reduce the incidence of hip fracture in the general population.
- ▶ Zoledronic acid, risedronate and alendronate reduce the incidence of hip fracture in the general population.
- ▶ The association between bisphosphonates and the incidence of hip fracture does not appear to be influenced by age.

How might these findings impact clinical practice in the foreseeable future?

- ▶ Bisphosphonates could be recommended as a first-line drug for the prevention and treatment of osteoporosis.
- ▶ Bisphosphonates could be used to decrease the risk of hip fracture among the general population.
- ▶ New clinical trials should address the association between bisphosphonates and the incidence of hip fracture among older populations with osteoporosis or osteopenia.

INTRODUCTION

Bisphosphonates can increase bone mineral density and reduce the incidence of vertebral and non-vertebral fractures; for this reason, bisphosphonates are common drugs for the treatment and prevention of osteoporosis and fracture, especially zoledronic acid.^{1–3} Approximately 40% of women and 15% of men 50 years or older will suffer major osteoporotic fractures during the remainder of their lifetimes,

and these fractures are associated with major morbidity.^{2,4,5} Hip fracture is a serious complication of osteoporosis.^{5,6} One-year mortality more than doubles after hip fracture.^{7–9} Therefore, it is important for clinical practice to explore effective methods for reducing the incidence of hip fracture (IHF) in patients with osteoporosis. Bisphosphonate treatment for osteoporosis might prevent hip fracture, but this needs to be confirmed.



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In fact, many studies exploring the effects of bisphosphonates on the IHF have been performed.^{10–29} These results have been reported hundreds of times, but the outcomes are not all the same. In recent years, there have been some meta-analyses and systematic reviews that included the effects of bisphosphonates on the IHF. In these meta-analyses and systematic reviews, bisphosphonates significantly reduced the IHF; however, none of them reported results stratified according to patient age or the kind of bisphosphonate used.^{1–3 30}

The incidence rate of osteoporosis or hip fracture in the elderly is higher than that in the general population. Osteoporotic hip fractures might be reduced by bisphosphonates in the elderly population, which has been reported in many studies but lacks a defined conclusion. To confirm that osteoporotic hip fractures can be prevented by bisphosphonates, especially in older individuals, a meta-analysis and systematic review was conducted.

METHODS

Bisphosphonate search method

Best-evidence research was conducted on bisphosphonates used to treat and prevent osteoporosis and fracture. We conducted a meta-analysis and systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and used a predetermined protocol.³¹ We systematically searched the MEDLINE (via PubMed), Embase, and Cochrane Library databases for all randomized placebo-controlled clinical trials of bisphosphonate drug treatment and prevention of osteoporosis and fracture published from database inception to January 10, 2021. Four researchers selected reports with clinical trials involving the treatment and prevention of osteoporosis and fracture with bisphosphonates. Reports that were not randomized, double-blind, placebo-controlled clinical trials or were unrelated to bisphosphonates were rejected. The selection included three stages: (1) review of titles, keeping those that would be potentially included; (2) review of titles and abstracts that remained from the first stage and retention of those that would be potentially included; and (3) reading the full texts of the articles that remained from the second stage and retention of those that could be included. Ultimately, 1536 articles remained in the third stage. To qualify for inclusion, studies had to be randomized controlled trials comparing interventions that compared the different bisphosphonates with placebos in adults (ages ≥ 50 , 65 years old).

Inclusion criteria

(1) Randomized, double-blinded, and placebo-controlled studies; (2) bisphosphonate treatments with the number of IHFs in the follow-up period; (3) use of bisphosphonates at the approved dosage for the treatment of osteoporosis or osteopenia; and (4) duration of ≥ 1 year.

Exclusion criteria

(1) Studies of other anti-osteoporosis drugs; (2) studies of patients who were treated with corticosteroids, generally because of underlying inflammatory diseases; (3) studies of patients with cancer; (4) evaluations using open-label drug

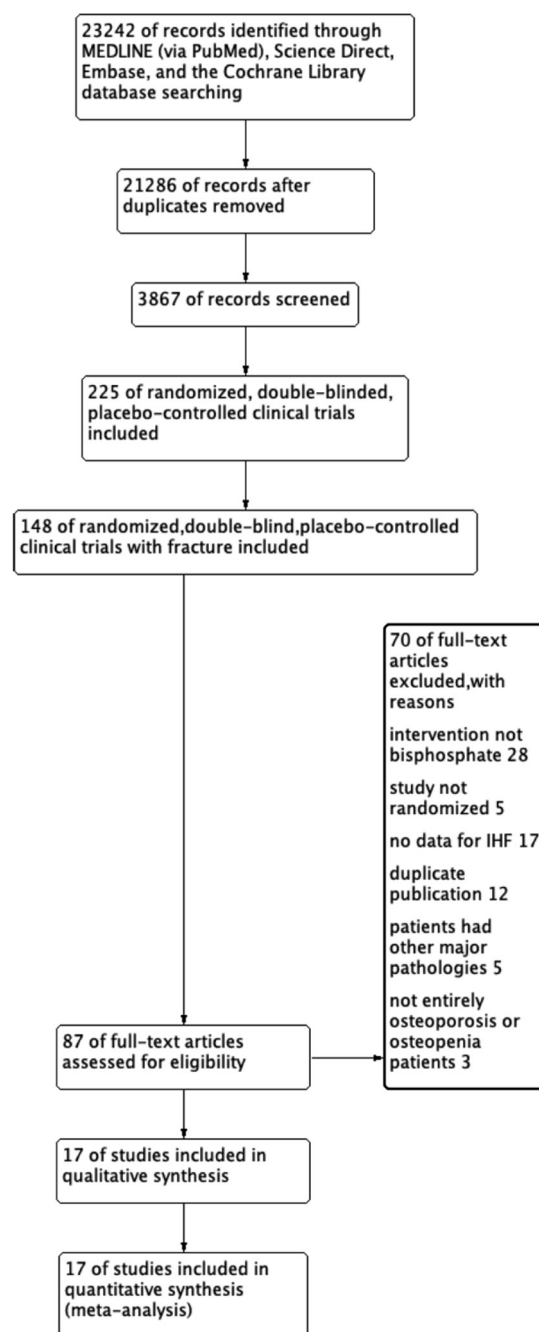


Figure 1 Study flow diagram. IHF, incidence of hip fracture.

treatments; and (5) duplicate reports; in these cases, only the final, complete trial results were reported.

Data extraction and verification

Data citations and abstracts identified from the searches were reviewed for inclusion and exclusion criteria by 2 reviewers (SZ and CZ), and full-text review and data extraction from published articles were reviewed by 2 researchers (SZ and WZ). The IHF was obtained from the texts of the articles by 2 investigators (TZ and LZ) and validated by 3 researchers (SZ, ZY, and DD).

Table 1 Descriptive data for the 17 qualifying trials

Source	Drug	Dose, mg	Duration, months	Participant treatment IHF	Placebo IHF	Mean age (range; years)	Region
Reid <i>et al</i> ²²	Zoledronic acid	5 mg 18 monthly	72 months	8/1000	12/1000	71 (≥65)	European, Pacific, Asia
Black <i>et al</i> ²⁴	Zoledronic acid	5 mg yearly	24 months	52/3875	88/3861	73 (65–89)	Europe, America, Asia
Nakamura <i>et al</i> ²⁰	Zoledronic acid	5 mg yearly	24 months	2/330	3/331	74 (65–89)	Japan
Bai ²⁶	Zoledronic acid	5 mg yearly	24 months	12/242	21/241	57	China
Ma	Zoledronic acid	5 mg yearly	36 months	8/327	13/333	55	China
Reginster ²⁷	Risedronate	5 mg daily	36 months	9/344	11/346	71	European, Pacific
Harris ¹⁹	Risedronate	5 mg daily	36 months	12/812	15/815	69	North America
McClung ¹⁸	Risedronate	2.5, 5 mg daily	36 months	137/6197	95/3134	≥70	North America, Europe, Pacific
Recker <i>et al</i> ²³	Ibandronate	0.5 mg, 1 mg, every 3 months	36 months	13/1912	11/950	67 (55–76)	USA, Europe
Harris ¹⁹	Etidronate	400 mg daily, 2 weeks every 3 months	36 months	1/212	2/211	65	USA
Storm <i>et al</i> ¹⁶	Etidronate	400 mg daily, 2 weeks every 3 months	36 months	1/33	2/33	68 (56–75)	USA, Denmark
Liberman ¹⁷	Alendronate	5 mg, 10 mg, 20 mg daily	24 months	1/597	3/397	64 (45–80)	America, Pacific, Europe, Israel
Black ²⁵	Alendronate	5 mg daily 24 months, 10 mg daily 24–36 months	36 months	11/981	22/965	70 (55–81)	USA
Cummings <i>et al</i> ¹⁵	Alendronate	5 mg daily 24 months; 10 mg daily 24–36 months	36 months	19/2218	24/2214	67 (55–80)	USA
Greenspan <i>et al</i> ¹⁴	Alendronate	10 mg daily	24 months	2/163	4/164	79 (≥65)	USA
McCloskey <i>et al</i> ¹²	Clodronate	800 mg daily	36 months	1/292	6/301	67	UK
Brusmsen <i>et al</i> ¹³	Pamidronate	150 mg daily	36 months	1/51	1/50	65 (40–75)	Netherlands

IHF, incidence of hip fracture.

Quality assessment

The quality of trials was assessed by Review Manager V.5.4 (Oxford, UK) according to the Cochrane Handbook for Systematic Reviews of Interventions. Discrepancies concerning extraction and/or assessment of the quality of data were addressed by the third person if necessary.

Statistical analysis

Risk ratios (RRs) were used to pool results for dichotomous outcomes. A two-sided *p* value of <0.05 was considered significant. The 95% CIs were provided for all pooled estimates. Subgroup analyses were performed according to different kinds of bisphosphonate and different age groups (≥55 years old or ≥65 years old). Heterogeneity among the studies was assessed by determining the Cochran *Q* and the *I*² statistic.³² For the *Q* statistic, *p*<0.10 was considered to indicate statistically significant heterogeneity. For the *I*² statistic, which indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, no heterogeneity was indicated by an *I*² of 0%–25%, moderate heterogeneity was indicated by an *I*² of 25%–50%, large heterogeneity was indicated by an *I*² of 50%–75%, and extreme heterogeneity was indicated by an *I*² of 75%–100%. A random-effects model of analysis was used (the DerSimonian-Laird method) for all pooled RRs in the means of outcomes. We performed the sensitivity analysis by removing the trials one by one. The asymmetry of the funnel plot was evaluated by Egger's test using the

p value. All statistical analyses were performed by Review Manager V.5.4 (Oxford, UK) and Stata V.16.0 software.

RESULTS

Search strategy

Our search strategy identified 23,242 unique publications, titles, and abstracts, which were screened for inclusion criteria. The full texts of 87 articles were retrieved, of which 17 met the inclusion criteria. The reasons for exclusion of the remaining articles were as follows: intervention was not bisphosphonate (28), the study was not randomized (5), duplicate publication (12), no data on the IHF (17), patients had other major pathologies (5) and patients were not entirely patients with osteopenia or osteoporosis (3). The study flow diagram is shown in figure 1.

Included studies

Table 1 shows descriptive data for the 17 qualifying trials. Bisphosphonates included zoledronic acid (ZOL), risedronate, alendronate, clodronate, pamidronate, ibandronate, and etidronate, and they were reported by 5, 3, 4, 1, 1, 1, and 2 articles, respectively. All studies were double-blind, placebo trials. Among the studies, 11 studies were registered in the international clinical medical center, and the settings of

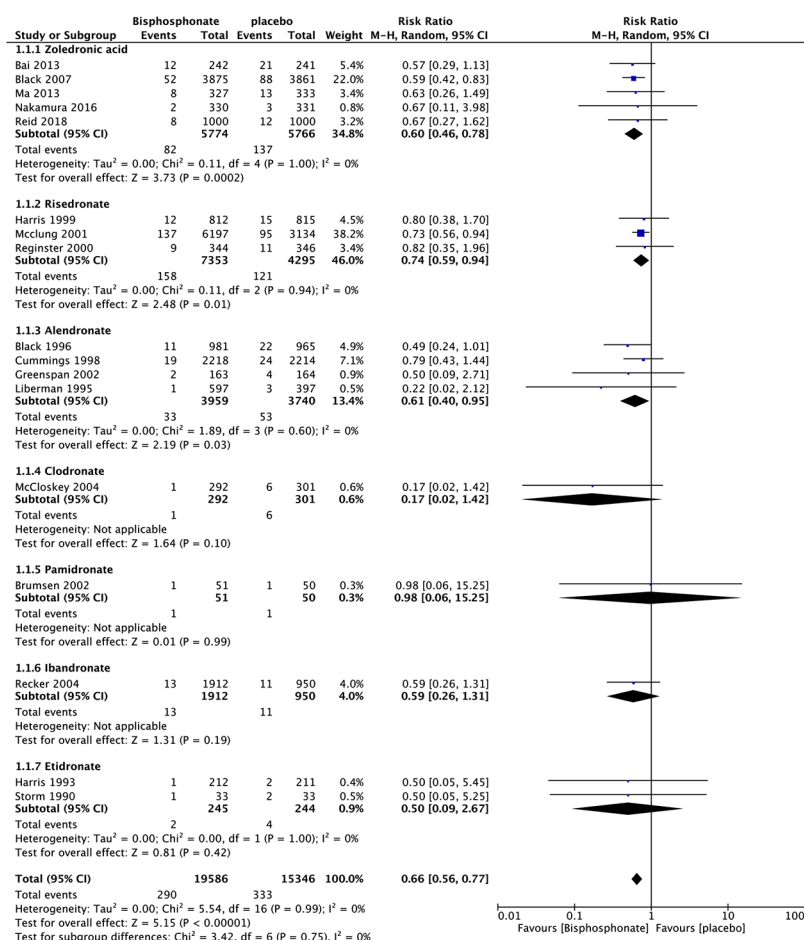


Figure 2 Total association between bisphosphonate therapy and IHF in the general population.

randomization, blinding, and placebos were listed on the website.^{10–13 18 20 22–24 27 29}

Total association between bisphosphonate therapy and the IHF in the general population

In the 17 pooled studies, 19,586 and 15,346 participants received bisphosphonates and placebo, respectively. Bisphosphonates significantly reduced the IHF (RR: 0.66; 95% CI: 0.56 to 0.77). ZOL, risedronate and alendronate significantly reduced the IHF (RR:

0.60; 95% CI: 0.46 to 0.78), (RR: 0.74; 95% CI: 0.59 to 0.94) and (RR: 0.61; 95% CI: 0.40 to 0.95), respectively, but clodronate, pamidronate, ibandronate and etidronate did not. The RRs and 95% CIs are shown in figure 2.

Overall association between bisphosphonate therapy and the IHF in patients ≥ 55 years old

In the 4 pooled studies, 5144 and 4162 participants received bisphosphonates and placebo, respectively. Bisphosphonates

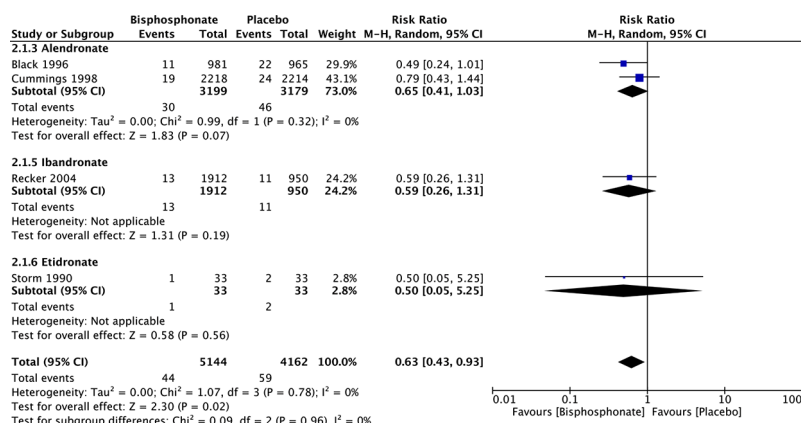


Figure 3 Overall association between bisphosphonate therapy and IHF in patients ≥ 55 years old.

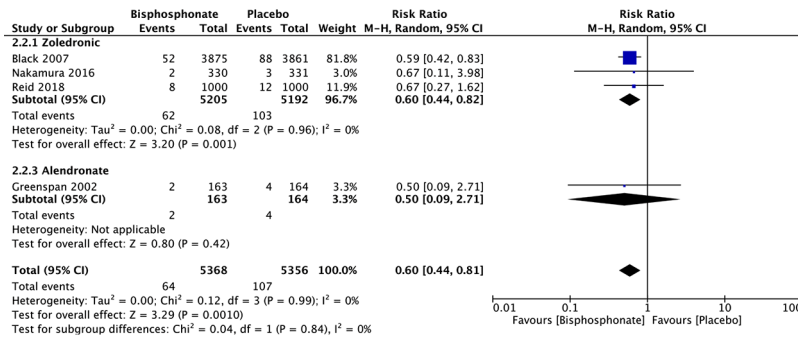


Figure 4 Overall association between bisphosphonate therapy and IHF in patients ≥ 65 years old.

significantly reduced the IHF (RR: 0.63; 95% CI: 0.43 to 0.93). The RRs and 95% CIs are shown in [figure 3](#).

Overall association between bisphosphonate therapy and the IHF in patients ≥ 65 years old

In the 4 pooled studies, 5368 and 5356 participants received bisphosphonates and placebo, respectively. Bisphosphonates significantly reduced the IHF (RR: 0.60; 95% CI: 0.44 to 0.81). Specifically, ZOL most significantly reduced the IHF (RR: 0.60; 95% CI: 0.44 to 0.82). The RRs and 95% CIs are listed in [figure 4](#).

Quality assessment

The results of the quality assessment are summarized in [figure 5](#), including the potential risk of individual studies ([figure 5A](#)) and the overall risk ([figure 5B](#)). Overall, the studies had a low risk of selection bias (random sequence generation), detection bias, attrition and reporting bias. The studies had an unclear risk of selection bias (allocation concealment) and performance bias.

Sensitivity analysis and publication bias

Sensitivity analysis using the leave-one-out approach found that the results were robust, as the removal of any one study did not dramatically change the direction or the significance of the results. Begg's and Egger's tests showed that there was no obvious publication bias ($t = -1.79$; $p = 0.093$; 95% CI: -0.87 to 0.75).

DISCUSSION

This meta-analysis and systematic review provided several pieces of evidence regarding the overall benefit of bisphosphonates on the IHF in different age groups and according to the kinds of bisphosphonates. In the 17 studies enrolled in these meta-analyses, only 2 studies showed that bisphosphonates (ZOL and risedronate) could significantly decrease the IHF.^{11 24} The other studies all showed that bisphosphonates did not significantly decrease the IHF, but none of them showed an increased IHF. Stratification according to age indicated that bisphosphonates could reduce the IHF in different age groups (≥ 55 years old and ≥ 65 years old). Stratification according to age and the kind of bisphosphonate showed that ZOL can reduce the IHF in ≥ 65 years age groups.

First, among all 17 studies, calcium and vitamin D were supplied to the treatment and placebo groups. Practice guidelines recommend calcium and vitamin D supplements

for older people to prevent fractures in patients with osteoporosis, which is the basis of the prevention and treatment of osteoporotic fractures. In most enrolled studies, participants received calcium and vitamin D supplements, indicating that these guidelines were generally accepted.³³

Second, in the 17 included studies, 5 used ZOL, 3 used risedronate, 4 used alendronate, 1 used clodronate, 1 used pamidronate, 1 used ibandronate and 2 used etidronate. In all enrolled studies, only 2 showed that bisphosphonates significantly decreased the IHF (ZOL and risedronate).^{18 24} In the other 15 trials, bisphosphonates did not significantly decrease the IHF. In the combination of the 17 trials, 19,586 patients received bisphosphonates and had 290 hip fracture events, whereas 15,346 received placebo and had 333 hip fracture events, and bisphosphonates significantly decreased the IHF ($p < 0.00001$). The effect of bisphosphonates on reducing the IHF was also found in previous meta-analyses and systematic reviews.^{1-3 30} All of these results confirmed that bisphosphonate reduction of the IHF should be defined.

Third, stratification according to age showed that bisphosphonates could significantly reduce the IHF in all age groups (≥ 55 years old and ≥ 65 years old). The previous meta-analyses and systematic reviews did not consider age.^{13 30} This meta-analysis and systematic review showed that the reduction in the IHF provided by bisphosphonates may not be affected by age.

Fourth, there were three generations of bisphosphonates: ZOL and risedronate represented the third generation, and alendronate represented the second generation. The manufacture of third-generation drugs is based on the two previous generations, while the manufacture of the second generation is based on the first. Third-generation or second-generation drugs might be better than first-generation drugs in at least some respects. In the total effectiveness of the meta-analyses and systematic reviews, the RRs (95% CI) of ZOL, risedronate and alendronate were 0.60 (0.46 to 0.78), 0.74 (0.59 to 0.94) and 0.61 (0.40 to 0.95), respectively. There were not enough data available to perform meta-analysis on the other bisphosphonates (ibandronate, etidronate, clodronate, pamidronate and tiludronate). It might be reasonable to state that ZOL, risedronate and alendronate are preferred for the prevention of hip fractures in patients with osteoporosis or osteopenia.

Finally, there were no data regarding the effect of ZOL on the IHF in individuals aged ≥ 70 years old. In clinical practice, patients with osteoporosis aged 70 years or older are

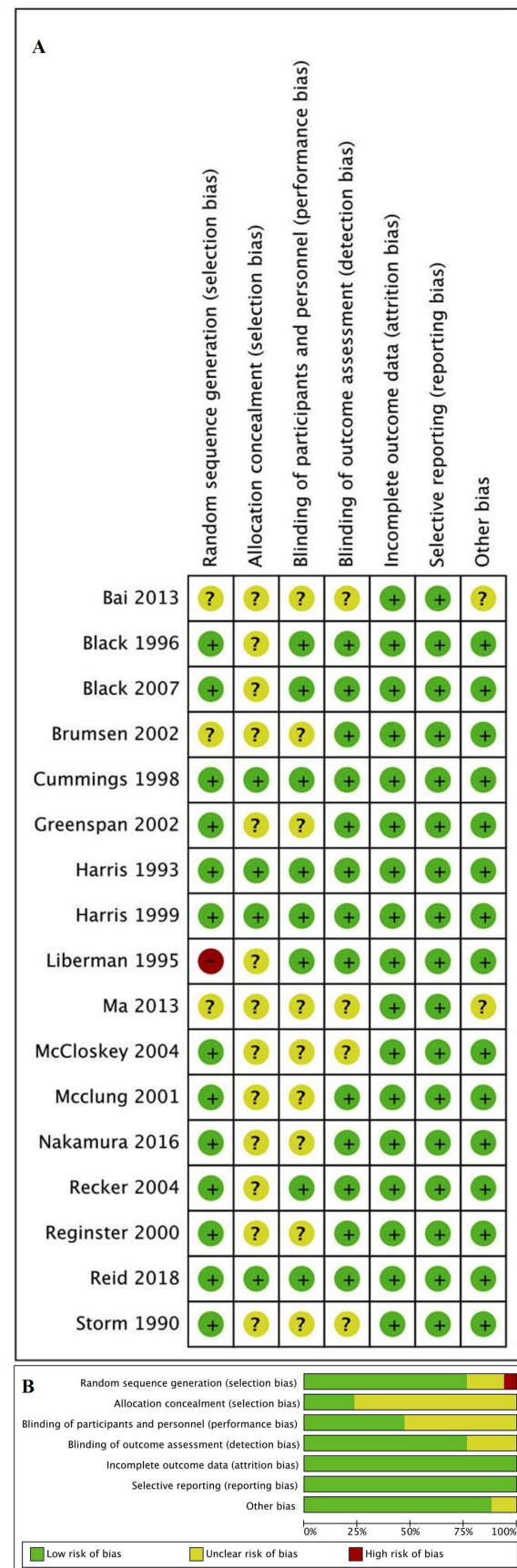


Figure 5 (A) Quality assessment of individual studies. (B) Assessment of each domain in Quality in Prognosis Studies (QUIPS) tool among the pooled studies.

often treated with ZOL. ZOL treatment for osteoporosis was used once yearly, while oral bisphosphonates were used daily or weekly. Therefore, compared with oral bisphosphonates, ZOL was more easily accepted by older patients. The incidence rate of hip fracture in the older population is higher than that in the younger population, and hip fracture is more harmful in older individuals than in younger individuals. Even if the effectiveness of ZOL on the IHF is the same as the others, ZOL should be preferred. Therefore, in the oldest population, the effectiveness of ZOL on the IHF should be researched or reported as a subgroup in related studies.

There were some limitations in these meta-analyses. First, the studies were all high quality, but some of them were inadequately reported, especially for the oldest patients. Second, there were some high-quality trials that researched bisphosphonate treatment and the prevention of osteoporosis or fracture but did not report the IHF as an endpoint. If the IHF was consistently reported as a detail, more valuable clinical information could be provided through meta-analyses. Third, there were few data on the relative information for men, which should be researched or reported in the future. Fourth, new clinical trials should address the association between bisphosphonates and the IHF among older populations with osteoporosis or osteopenia, especially among individuals ≥ 70 years old.

In summary, systematic reviews and meta-analyses showed that bisphosphonates (especially ZOL, alendronate and risedronate) could significantly decrease the IHF. ZOL-mediated reduction of the IHF might not be influenced by age, but it should be confirmed in populations aged ≥ 70 years old.

Contributors SZ, CZ, and DD conceived and designed the experiments. SZ, TZ, and JX performed the experiments. SZ, LZ, and WZ analyzed the data. ZY, LJ, and MG contributed reagents/materials/analysis tools. SZ wrote the paper. SZ is the guarantor of the entire study.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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