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**Title:** Efficacy and Safety of Zoledronate for Osteopenia and Osteoporosis in Postmenopausal Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

**Running Title:** Zoledronate for Osteopenia and Osteoporosis in Postmenopausal Women

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## Clinical Question Box

Is Zoledronate Recommended for Osteopenia and Osteoporosis Prevention in Postmenopausal Women?

High-certainty evidence supports the use of zoledronate in preventing various types of fractures. Additionally, moderate-certainty evidence indicates that zoledronate improves bone mineral density without increasing serious adverse events compared to placebo. Therefore, zoledronate is strongly recommended for preventing osteoporosis in postmenopausal women.

## Abstract

**Introduction**: Osteopenia and osteoporosis are common among postmenopausal women, significantly increasing fracture risk and reducing bone mineral density (BMD). Zoledronate, a long-acting bisphosphonate, has shown promise in fracture prevention and BMD improvement. However, its efficacy and safety in osteopenic and osteoporotic populations remain subjects of debate.

**Methods**: A comprehensive search was conducted in PubMed, Embase, the Cochrane Library, and Web of Science up to January 2025, focusing on randomized controlled trials (RCTs) comparing zoledronate with a placebo. The primary outcome was fracture prevention (any type). Pooled odds ratios (ORs) and mean differences (MDs) with 95% confidence intervals (CIs) were calculated.

**Results**: Ten RCTs comprising 12,771 postmenopausal women met the inclusion criteria. Zoledronate significantly reduced overall fracture risk (OR: 0.61, 95% CI: 0.55–0.69, $p < 0.001$), with consistent benefits in both osteopenic and osteoporotic populations. The risk of vertebral fractures was also significantly reduced in osteopenic (OR: 0.49, 95% CI: 0.35–0.71, $p < 0.001$) and osteoporotic (OR: 0.34, 95% CI: 0.18–0.65, $p = 0.001$) subgroups. Zoledronate significantly improved BMD at the lumbar spine (MD: 6.26%, 95% CI: 5.48–7.03, $p < 0.001$), total hip (MD: 5.30%, 95% CI: 4.61–5.98, $p < 0.001$), and femoral neck (MD: 3.84%, 95% CI: 2.60–5.09, $p < 0.001$). The incidence of adverse events was comparable between the zoledronate and placebo groups (OR: 1.06, 95% CI: 0.80–1.40, $p = 0.70$).

**Conclusion**: Zoledronate is an effective and well-tolerated option for preventing fractures and improving BMD in postmenopausal women with osteopenia or osteoporosis. Its long-acting nature enhances adherence, supporting its broader use in clinical practice.

**Keywords**: Zoledronate, Osteoporosis, Osteopenia, Postmenopausal, Fracture Prevention, Meta-analysis

## Introduction

Osteopenia and osteoporosis are significant global health concerns, particularly among postmenopausal women due to estrogen deficiency.[1] According to the World Health Organization (WHO), osteoporosis is diagnosed when bone mineral density (BMD) is 2.5 standard deviations (SD) or more below the average BMD of a young adult reference population (T-score ≤ -2.5). In contrast, osteopenia is classified as a BMD reduction between 1.0 and 2.5 SD below the young adult mean (T-score between -1.0 and -2.5). The U.S. Centers for Disease Control and Prevention (CDC) reports that 12.6% of adults aged 50 and older have osteoporosis, with a higher prevalence in women (19.6%) than in men (4.4%). Furthermore, 43.1% of individuals in this age group have low bone mass, encompassing both osteopenia and osteoporosis.[2] Research indicates that nearly half of postmenopausal women have osteopenia, increasing their risk of progressing to osteoporosis and experiencing fractures.[3] The vertebrae, hip, and wrist are the most common fracture sites, with hip fractures being particularly severe, contributing to a one-year mortality rate of 20–30% and an increased risk of long-term disability.[4] Even in the absence of fractures, osteopenia has been associated with reduced health-related quality of life, likely due to functional limitations, fear of falling, and decreased physical performance.[5] Fractures related to osteoporosis and osteopenia not only impose a significant health burden on individuals but also present a substantial economic challenge to healthcare systems.[6] In the United States alone, osteoporosis-related fractures are projected to drive healthcare expenditures beyond $25.3 billion annually by 2025.[7] With an aging population and rising life expectancy, the prevalence of osteoporosis, osteopenia, and associated fractures is expected to increase, underscoring the urgent need for proactive prevention and management strategies.

Various strategies are employed for the prevention and management of osteoporosis and osteopenia, incorporating both pharmacological and non-pharmacological approaches. Non-pharmacological interventions primarily focus on lifestyle modifications, including regular weight-bearing and muscle-strengthening exercises, as well as fall prevention measures, which play a crucial role in reducing fracture risk.[8] Pharmacological treatments are recommended for individuals at high fracture risk, aiming to enhance BMD, inhibit bone resorption, or promote bone formation. These treatments include selective estrogen receptor modulators such as raloxifene, which mimics estrogen's protective effects on bone; denosumab, a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-b ligand (RANKL) to suppress bone turnover; parathyroid hormone analogs like teriparatide and abaloparatide, which stimulate bone formation and are reserved for severe cases; and romosozumab, a sclerostin inhibitor that simultaneously enhances bone formation and reduces resorption.[9,10]

Among pharmacological treatments, bisphosphonates remain the first-line therapy, with zoledronate being one of the most potent agents.[11] It effectively inhibits osteoclast-mediated bone resorption, thereby enhancing bone strength. A major advantage of zoledronate is its intravenous administration, which can be given once yearly or once every two years, significantly improving adherence compared to oral bisphosphonates that require strict dosing schedules and are associated with gastrointestinal side effects.[12] Large-scale trials, such as the HORIZON-PFT study, have demonstrated that zoledronate substantially reduces fracture risk—by 70% for vertebral fractures, 41% for hip fractures, and 25% for non-vertebral fractures over three years in postmenopausal women with osteoporosis.[13] Furthermore, emerging evidence suggests that zoledronate may also benefit individuals with osteopenia by slowing disease progression and reducing fracture risk in

high-risk populations.[14,15] These findings underscore the importance of early diagnosis and intervention to prevent long-term complications associated with low bone mass.

Although zoledronate is widely used, evidence regarding its efficacy and safety in osteoporosis prevention, rather than treatment, remains limited. Most research has focused on its use in patients with established osteoporosis, while fewer meta-analyses have systematically examined its role in fracture prevention and bone mineral density improvement among postmenopausal women without diagnosed osteoporosis.[16,17] This systematic review and meta-analysis aim to synthesize data from randomized controlled trials (RCTs) to assess the efficacy and safety of zoledronate in osteopenia and osteoporosis among postmenopausal women. By integrating existing evidence, this study seeks to provide valuable insights into the clinical utility of zoledronate, supporting healthcare professionals in making informed decisions about its role in osteoporosis prevention.

## Methods

### *Overview*

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] This study did not involve human participants. The systematic review protocol was registered in the Open Science Framework.[19]

### *Eligibility Criteria*

The inclusion criteria were: 1) postmenopausal women diagnosed with primary osteopenia or osteoporosis, 2) treatment with zoledronate or placebo as the intervention, and 3) studies limited to randomized controlled trials (RCTs). The exclusion criteria were: 1) sequential treatment with zoledronate after denosumab, 2) studies evaluating zoledronate in patients with cancer or bone metastases, 3) studies lacking efficacy or safety outcomes, and 4) subgroup analyses of previously published studies.

### *Search Strategy*

A comprehensive literature search was conducted using the following databases: PubMed, Embase, Cochrane Library and Web of Science. The search included studies without language restrictions up to January 20, 2025. The search strategy, based on the PICO framework, used the keywords “postmenopausal” for patients, “zoledronate” or “zoledronic acid” for the intervention, and “randomized” to limit the results to RCTs.

### *Study Selection and Data Extraction*

All retrieved articles were imported into EndNote for duplicate removal. Two independent reviewers (J.L. and W.L.) screened the titles and abstracts. Full-text articles of potentially eligible studies were then assessed for final inclusion. Any disagreements were resolved through discussion or consultation with a third reviewer (Z.Z.). A standardized data extraction form was used to collect study characteristics (first author, publication year, study design, sample size, and study duration), participant characteristics (age), intervention details (zoledronate dosage, administration frequency, and treatment duration), comparison groups (placebo or other pharmacological interventions), and outcomes (fracture incidence, changes in BMD, and adverse events). Data were extracted independently by two reviewers and cross-checked for accuracy.

*Outcomes*

The primary outcome was the prevention of any type of fracture. The secondary outcomes included changes in BMD in the lumbar spine, total hip, and femoral neck as well as the occurrence of adverse events and serious adverse events. A subgroup analysis was conducted for the primary outcome, comparing osteoporosis and osteopenia. Additionally, vertebral fracture prevention was assessed separately for osteoporosis and osteopenia.

*Data Synthesis and Statistical Analysis*

Meta-analysis was conducted using Review Manager (RevMan) software. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, while mean differences (MDs) with 95% CIs were used for continuous outcomes. Heterogeneity was assessed using the $I^2$ statistic, categorized as low (≤25%), moderate (25–50%), or high (>50%).[20] A random-effects model was applied when significant heterogeneity was present ($I^2$ > 50%); otherwise, a fixed-effects model was used. Subgroup analyses were performed based on

treatment duration, zoledronate dosage, and baseline BMD. Sensitivity analyses were conducted by excluding studies with a high risk of bias.

*Risk of Bias and Certainty of Evidence Assessment*

The risk of bias for each included RCT was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating five key domains: randomization process, deviations from the intended intervention, missing outcome data, outcome measurement, and selection of reported results.[21] Publication bias was evaluated using funnel plots. The overall certainty of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, considering factors such as study limitations, result consistency, precision, and potential publication bias.[22]

## Results

*Study Characteristics*

After searching the databases, 2,401 studies were identified. Following the removal of duplicates (376 studies), initial screening (1,626 studies), and full-text screening (37 studies), a total of 12 studies were included in the final analysis (Figure S1). Two studies reporting short-term outcomes were also excluded.[23,24] Ultimately, this systematic review and meta-analysis included 10 RCTs involving 12,771 postmenopausal women (Table 1).[15,25-33] The studies were conducted in China, New Zealand, and international cohorts, with follow-up periods ranging from 1 to 10 years. The mean age of participants ranged from 55 to 73 years, and inclusion criteria were based on BMD T-scores, with five studies including individuals with osteopenia (T-score between -1.0 and -2.5) and five studies focusing on osteoporosis (T-score ≤ -2.5) at various skeletal sites. Zoledronate was administered at intervals ranging from annually to every 18 months, with placebo groups serving as the comparator.

*Fracture Prevention*

Three studies, including 8,879 patients, demonstrated that zoledronate significantly reduced the risk of any type of fracture in osteoporosis patients, with an OR of 0.62 (95% CI 0.54–0.71, $p < 0.001$; $I^2 = 0\%$) (Figure 1). Another three studies, including 2,819 patients, evaluated the efficacy of zoledronate in preventing any type of fracture in osteopenia patients, reporting an OR of 0.61 (95% CI 0.50–0.74, $p < 0.001$; $I^2 = 0\%$). A pooled analysis across all postmenopausal women showed an overall reduction in fracture risk, with an OR of 0.61 (95% CI 0.55–0.69, $p < 0.001$; $I^2 = 0\%$).

Subgroup analysis for vertebral fracture prevention is presented in Figure S2. Two studies, including 8,219 patients, demonstrated that zoledronate significantly reduced the risk of vertebral fractures in osteoporosis patients, with an OR of 0.34 (95% CI 0.18–0.65, $p = 0.001$; $I^2 = 48\%$). Another two studies, including 2,703 patients, assessed zoledronate's efficacy in preventing vertebral fractures in osteopenia patients, yielding an OR of 0.49 (95% CI 0.35–0.71, $p < 0.001$; $I^2 = 0\%$). A pooled analysis in postmenopausal women showed an overall reduction in vertebral fracture risk, with an OR of 0.40 (95% CI 0.27–0.60, $p < 0.001$; $I^2 = 61\%$).

*Effect on BMD*

Seven studies, including 11,055 patients, demonstrated that zoledronate effectively improved BMD in the lumbar spine, with an MD of 6.26% (95% CI 5.48–7.03, $p < 0.001$; $I^2 = 100\%$) (Figure 2). Eight studies, including 11,305 patients, confirmed its effectiveness in increasing BMD in the total hip, with an MD of 5.30% (95% CI 4.61–5.98, $p < 0.001$; $I^2 = 100\%$). Additionally, three studies, including 8,236 patients, showed that zoledronate significantly improved femoral neck BMD, with an MD of 3.84% (95% CI 2.60–5.09, $p < 0.001$; $I^2 = 100\%$). A pooled analysis across these three skeletal sites indicated an overall MD of 5.47% (95% CI 5.10–5.85, $p < 0.001$; $I^2 = 100\%$). Heterogeneity could not be reduced by sensitivity analysis.

*Risk of Adverse Events*

The risk of any adverse events is shown in the supplementary materials, with an OR of 1.06 (95% CI 0.80–1.40, $p = 0.70$; $I^2 = 80\%$) (Figure 3A). Similarly, the risk of serious adverse events is presented in the supplementary materials, with an OR of 0.93 (95% CI 0.67–1.31, $p = 0.69$; $I^2 = 67\%$) (Figure 3B). Sensitivity analysis for the risk of any adverse events yielded an OR of 1.22 (95% CI 1.06–1.40, $p = 0.005$; $I^2 = 0\%$) (Figure S3), while sensitivity analysis for the risk

of serious adverse events showed an OR of 1.06 (95% CI 0.77–1.46, p = 0.70; $I^2$ = 56%) (Figure S4).

*Subgroup Analysis by Treatment Duration*

Subgroup analyses based on treatment duration were conducted for both fracture prevention and bone mineral density (BMD) outcomes. Zoledronate administration for 1 year and more than 1 year demonstrated significant efficacy in reducing fracture risk, with odds ratios of 0.62 (95% CI: 0.54–0.71, p < 0.001; $I^2$ = 0%) and 0.60 (95% CI: 0.49–0.73, p < 0.001; $I^2$ = 0%), respectively (Figure S5).For lumbar spine BMD, zoledronate use for 1 year and more than 1 year resulted in mean differences (MDs) of 5.68% (95% CI: 5.27–6.09, p < 0.001; $I^2$ = 99%) and 7.46% (95% CI: 6.98–7.95, p < 0.001; $I^2$ = 99%), respectively (Figure S6). Similarly, improvements in total hip BMD were observed with MDs of 4.38% (95% CI: 3.29–5.47, p < 0.001; $I^2$ = 100%) for 1-year treatment and 6.84% (95% CI: 6.51–7.16, p < 0.001; $I^2$ = 99%) for treatment exceeding 1 year (Figure S7).

*Publication Bias and Risk of Bias*

Assessment of publication bias using funnel plots and Egger's test revealed no significant asymmetry for most outcomes, including fracture prevention, lumbar spine BMD, and adverse events (Figures S8–S14). However, a notable asymmetry was observed for the outcome of Total Hip BMD, suggesting potential publication bias. The risk of bias assessment conducted using the Cochrane Risk of Bias 2 tool indicated that most studies had a low risk of bias (Figure S15). However, one study had a high risk of bias due to incomplete follow-up, while another exhibited a high risk of performance and detection bias. The certainty of evidence is provided in the supplementary materials. There is high certainty of evidence for zoledronate in preventing

fractures and moderate certainty in improving BMD. While moderate evidence supports no increase in serious adverse events, there is evidence of an increase in any kind of adverse events.

## Discussion

This systematic review and meta-analysis provide robust evidence that zoledronate is highly effective in preventing osteoporosis and osteopenia in postmenopausal women. The findings demonstrate a significant reduction in fracture risk and notable improvements in BMD in both osteoporotic and osteopenic populations. Specifically, zoledronate significantly reduced the risk of fractures in osteopenic patients, reinforcing its potential as an early intervention strategy for those at risk of progressing to osteoporosis. Additionally, subgroup analysis demonstrated its efficacy in reducing vertebral fractures in osteopenic patients, further supporting its role in preserving bone health. These results align with previous large-scale clinical trials supporting the efficacy of zoledronate in osteoporosis treatment,[26] but this study extends the evidence base by demonstrating its preventive benefits in osteopenia. The findings are consistent with prior studies highlighting zoledronate's long-acting antiresorptive effects, reinforcing its position as a key agent for early intervention in bone health management.[34] Moreover, this analysis provides a more comprehensive synthesis of RCTs, strengthening the certainty of evidence regarding its preventive benefits across different levels of bone mass reduction.

These findings suggest that clinicians should consider zoledronate as a first-line option not only for postmenopausal women with osteoporosis but also for those with osteopenia, particularly those at higher fracture risk based on BMD and clinical factors. Pharmacological strategies for fracture prevention in osteopenia and osteoporosis follow a stepwise approach based on fracture risk, BMD, and patient-specific factors. First-line therapy typically includes bisphosphonates (e.g., zoledronate, alendronate, and risedronate), which inhibit bone resorption and are recommended for most patients at high risk of fractures.[35] If bisphosphonates are contraindicated or poorly tolerated, denosumab, a monoclonal antibody targeting RANKL, serves as an alternative option,

particularly in individuals with renal impairment.[34] In cases of severe osteoporosis or multiple fractures, anabolic agents such as teriparatide or romosozumab are prioritized to stimulate bone formation before transitioning to antiresorptive therapy for maintenance. Hormone replacement therapy or selective estrogen receptor modulators may be considered for postmenopausal women with low BMD but without high fracture risk.[36] The selection and sequencing of these agents depends on balancing efficacy, safety, and patient comorbidities, ensuring optimal long-term bone health.

Despite the strong evidence supporting zoledronate's efficacy in both osteoporosis and osteopenia, further research is warranted to explore its long-term effects beyond the follow-up periods assessed in the included studies. Future studies should investigate its optimal dosing interval, particularly whether extended dosing regimens could maintain benefits while further minimizing potential adverse events. Additionally, comparative studies evaluating zoledronate against newer osteoporosis therapies, such as monoclonal antibodies and anabolic agents, are needed to refine treatment guidelines. From a health policy perspective, incorporating zoledronate into osteoporosis and osteopenia prevention programs could significantly reduce the incidence of fractures and associated healthcare costs. Policymakers should consider strategies to increase access to zoledronate, particularly in aging populations where osteoporosis-related fractures impose a substantial economic burden.

This study has several limitations that should be acknowledged. Although the analysis included randomized controlled trials, variations in study designs, follow-up durations, and baseline characteristics of the participants may have contributed to heterogeneity. Second, although no significant increase in serious adverse events was observed, the potential for rare but

serious complications, such as atypical femoral fractures and osteonecrosis of the jaw, underscores the need for ongoing long-term surveillance.

## Conclusion

This meta-analysis provides robust evidence that zoledronate is an effective and well-tolerated option for osteoporosis and osteopenia prevention in postmenopausal women, significantly reducing fracture risk and improving BMD without a notable increase in serious adverse events. Its long-acting nature enhances treatment adherence, making it a practical choice for early bone health management.

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**Data Availability:** The corresponding author will make the datasets available upon reasonable request.

**Ethical Statement:** Institutional Review Board approval was waived due to the nature of the meta-analysis.

**Conflict of Interest:** The authors report no conflicts of interest in this work.

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Table 1: Summary of Included Studies

| Author Year | Country | Follow-up | Interval | Zoledronate | Placebo | Age (years) | Inclusion Criteria |
|---|---|---|---|---|---|---|---|
| Bai 2013[a] | China | 2 years | 1 year | 242 | 241 | 56.8 | BMD T-score ≤ -2.5 at the femoral neck without vertebral fractures, or ≤ -1.5 with ≥2 vertebral fractures |
| Black 2007 | International | 3 years | 1 year | 3,875 | 3,861 | 73.1 | BMD T-score ≤ -2.5 at the femoral neck without vertebral fracture, or ≤ -1.5 with ≥2 mild or ≥1 moderate vertebral fracture |
| Bolland 2025 | New Zealand | 10 years | 12 to 18 months | 352 | 351 | 56.1 | -2.5 ≤ BMD T-score ≤ 0 at the lumbar spine, femoral neck, or total hip |
| Chao 2013[a] | China | 3 years | 1 year | 327 | 333 | 55 | BMD T-score of ≤ -2.5 SD at the lumbar spine or total hip |
| Grey 2010 | New Zealand | 5 years | 1 year | 20 | 21 | 63.5 | -2.0 ≤ BMD T-score ≤ -1.0 at the total hip or femoral neck |
| Grey 2014 | New Zealand | 5 years | 18 months | 41 | 34 | 65.5 | -2.5 ≤ BMD T-score ≤ -1.0 at the total hip or femoral neck |
| Liang 2017 | China | 2 years | 1 year | 155 | 95 | 57.3 | -3.3 ≤ BMD T-score of ≤ -2.5 SD at the lumbar spine or total hip |
| McClung 2009[a] | International | 2 years | 1 year | 198 | 202 | 60.2 | -2.5 < BMD T-score ≤ -1.0 at the lumbar spine with BMD T-score > -2.5 at the femoral neck |
| Reid 2018 | New Zealand | 6 years | 18 months | 1,000 | 1,000 | 71 | -2.5 ≤ BMD T-score ≤ -1.0 at the total hip or femoral neck |
| Yang 2015[a] | China | 1 year | 1 year | 50 | 50 | 60.6 | BMD T-score of ≤ -2.5 SD at the lumbar spine or total hip |

a: Using additional calcium and vitamin D in both groups

BMD: Bone Mineral Density

Table 2: Summary of Certainty of Evidence

| Outcomes | Impact | Number of Participants (Studies) | Certainty of the Evidence (GRADE) |
|---|---|---|---|
| Fracture prevention (any type) | Odds Ratio: 0.61 (95% CI 0.55, 0.69), $p < 0.01$ | 11,698 (7 studies) | ⊕⊕⊕⊕ High |
| Improvement in bone mineral density | Mean Difference 5.47% (95% CI 5.10, 5.85), $p < 0.001$ | 11,305 (8 studies) | ⊕⊕⊕⊖ Moderate |
| Risk of any adverse event | Odds Ratio: 1.06 (95% CI 0.80, 1.40), $p = 0.70$ | 11,982 (6 studies) | ⊕⊕⊕⊖ Moderate |

GRADE: Grading of Recommendations, Assessment, Development, and Evaluations

Figure 1: Comparison of Zoledronate vs. Placebo for Any Fracture Prevention

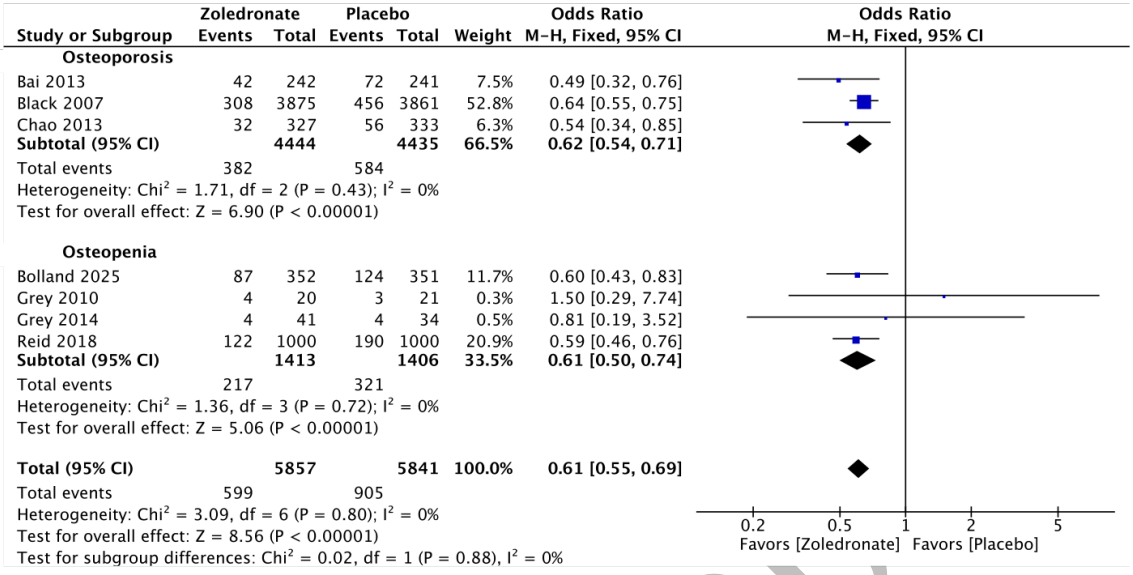


Figure 2: Effectiveness of Zoledronate in Improving Bone Mineral Density

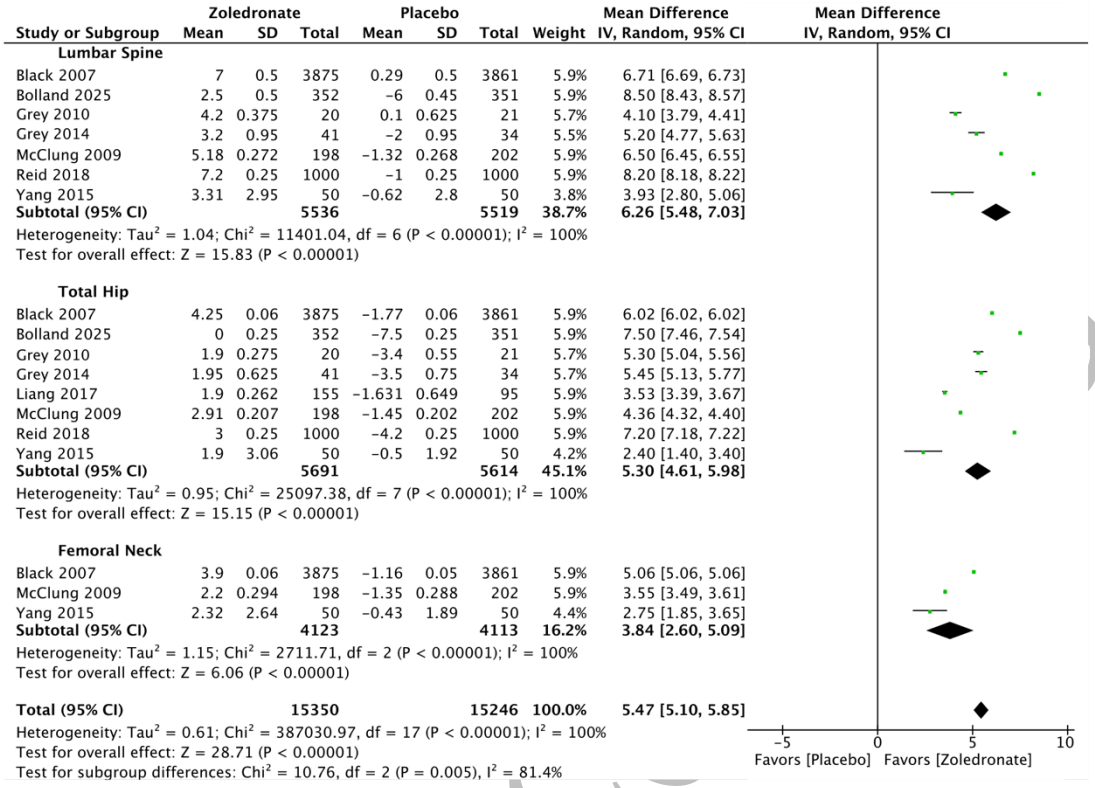
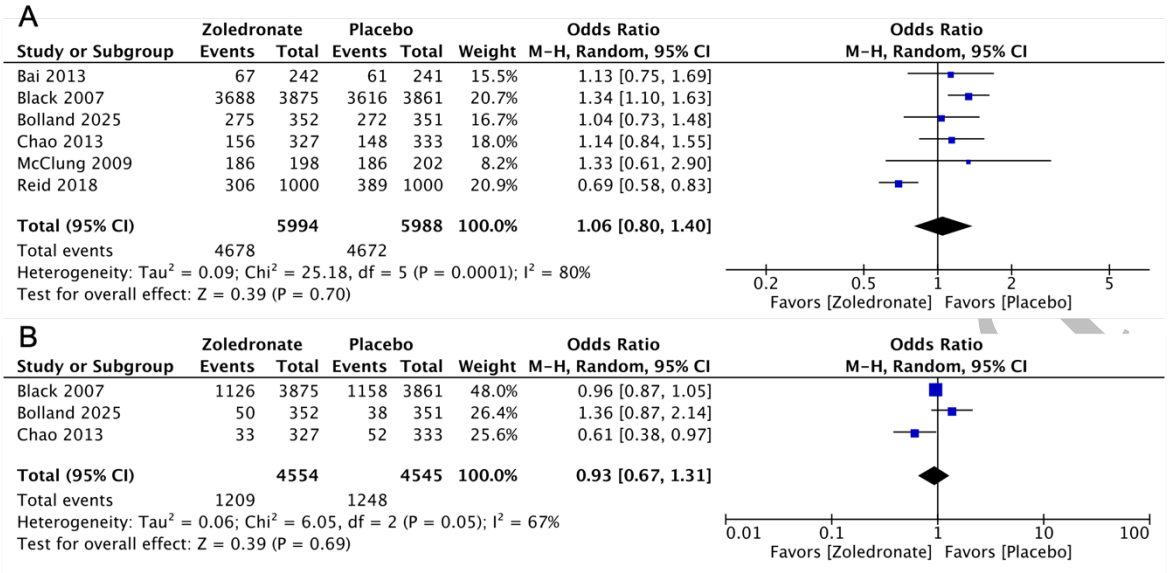


Figure 3: Risk of Adverse Events: Zoledronate versus Placebo




A: Any Adverse Event; B: Serious Adverse Event