Efficacy and safety of bisphosphonates for postmenopausal women:

A systematic review and network meta-analysis

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the Master of Science degree in the School of Epidemiology and Public Health

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ABSTRACT

Fragility fractures caused by loss of bone mass due to postmenopausal osteoporosis represent a growing morbidity worldwide. Bisphosphonates are first-line medications for fracture treatment and prevention. In the first phase, we updated a Cochrane systematic review of randomized controlled trials on alendronate, assessing its efficacy for five types of fracture prevention, quality of life, and various safety outcomes. In the second phase, we combined indirect and direct evidence to perform a network meta-analysis including alendronate and nine other bisphosphonates evaluating the comparative efficacy and safety of these treatments. Overall, 58 studies were included in the review and 83 studies in the network. Most evidence was of moderate to high quality. Alendronate and zoledronic acid were effective for preventing the most types of fractures, while off-label and unapproved bisphosphonates showed poor efficacy. More evidence is required to evaluate long-term treatment and rare adverse events.

ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my supervisor Dr. George Wells for giving me the opportunity to work on this project, and for his invaluable guidance, continuous counsel and immense knowledge. I am indebted to the rest of my advisory committee, Dr. Peter Tugwell for his knowledge and support, and Shuching Hsieh for her work on the project. I am grateful for her abundant review experience and our many discussions on the nuances of data extraction. Thank you to Said Abdelrazeq, Wenfei Liu, Joan Peterson and Annie Bai for their help and time on screening, extraction and quality assessments, and Nazmun Nahar for showing me shortcuts to formatting tables. I am grateful to Lily Chen and Alomgir Hossain for answering my questions on the statistical analysis. Lastly but not least, nobody has been more important to me in the pursuit of this project than my family, whom I would like to thank for their understanding, encouragement and emotional support.

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CHAPTER 1: INTRODUCTION

1.1 RATIONALE

Osteoporosis, a term describing “porous bone”, is the consequence of an imbalance between increased bone resorption and decreased bone formation. It is a systemic skeletal disease characterized by loss of bone strength and deterioration of bone microarchitecture leading to increased risk of fragility fractures. Osteoporosis is highly prevalent, affecting an estimated 1.5 million Canadians over age 40 (1) and causing 8.9 million fractures annually worldwide (2). Fragility fractures from low-energy falls are associated with high costs to the individual as well as healthcare systems. The global burden of osteoporosis is expected to increase with rapid projected growth of the aging population.

Bisphosphonates are analogs of natural inorganic pyrophosphates that inhibit bone resorption (3) and are indicated for osteoporosis treatment or prevention in most countries. Seven bisphosphonates have been approved worldwide for osteoporosis: alendronate, risedronate, etidronate, ibandronate, zoledronic acid, minodronate and clodronate. Other bisphosphonates approved for other bone diseases such as pamidronate, neridronate and tiludronate have also been used off-label for osteoporosis.

Agencies such as the Food and Drugs Administration (FDA) mandate placebo as a control for approval of a new intervention (4). Additionally, due to the low incidence of fractures, long-term followup durations and large sample sizes are usually required to provide adequate power to these trials (5). As a result, few head-to-head trials have been designed to compare the efficacy of bisphosphonates against other bisphosphonates or antiosteoporotic treatments. Network meta-analyses which allow the utilization of both direct and indirect evidence have been conducted previously to provide pooled estimates of comparative efficacy, but they did not examine in adequate detail certain safety outcomes, patient quality of life, combinations of bisphosphonate treatments, or the most frequent fracture sites (*e.g.,* non-vertebral, vertebral, wrist, hip). A comprehensive network meta-analysis is required to fill existing gaps in knowledge.

The rationale of this thesis is to summarize and synthesize the comparative efficacy and safety of bisphosphonate and bisphosphonate combination treatments. We will conduct a systematic review on alendronate compared to placebo and other active pharmacologics for osteoporosis among postmenopausal women. We chose alendronate as the intervention of interest for the systematic review because it is the most frequently prescribed first-line oral bisphosphonate, and one of the earliest approved treatments for osteoporosis. It has the highest market share for prescriptions of oral bisphosphonates dispensed from US outpatient retail pharmacy settings, accounting for 83% of all dispensed oral bisphosphonates in 2002 and 72% in 2012 (6). It is often recommended in clinical practice guidelines as one of the first osteoporosis treatments for postmenopausal women at risk of fracture (7). Hence, it was the most likely intervention to be compared in head-to-head trials, thereby allowing it to be representative of the available direct evidence in literature. A systematic review of alendronate compared to placebo and to active pharmacologic treatments would be clinically important and would also significantly contribute towards execution of the second thesis objective, conducting a comprehensive network meta-analysis of alendronate and nine other bisphosphonates for osteoporosis. Results of the systematic review will provide a summary of the direct evidence base regarding the most frequently used bisphosphonate, and will be compared to network meta-analysis estimates based on both direct and indirect evidence assessing the relative efficacy and safety of bisphosphonates for fracture prevention.

1.2 THESIS OBJECTIVES

The objectives of the thesis are:

i. To conduct a systematic review and meta-analysis to assess the efficacy and safety of alendronate in the prevention of osteoporotic fractures in postmenopausal women.
ii. To utilize a series of indirect and direct comparisons in a network meta-analysis for each outcome to assess the efficacy and safety of a group of bisphosphonate treatments in the prevention of osteoporotic fractures in postmenopausal women.

1.3 CHAPTER OUTLINE

The thesis is divided into 5 chapters.

Chapter 1: This is an introductory chapter that provides the rationale, thesis objectives, and an overview of subsequent chapters.

Chapter 2: The second chapter provides a summary of the pathophysiology of postmenopausal osteoporosis, burden of disease, diagnostic criteria, and pharmacologic treatments for the condition.

Chapter 3: This chapter presents the systematic review and meta-analysis of trials assessing alendronate. First, the methods are described, including the eligibility criteria for inclusion, search methods, data management, extracted information, risk of bias assessments, data analysis, subgroup analysis and sensitivity analysis. Next, results of the analysis are presented. General characteristics and risk of bias assessments of included studies are summarized, followed by results of the main analysis, subgroup analysis and sensitivity analysis for efficacy and safety outcomes. The findings are summarized and interpreted in the context of relevant literature. Finally, strengths and limitations of the review are described.

Chapter 4: This chapter describes a series of network meta-analyses including approved and off-label bisphosphonates. First, the methods are described, detailing the eligibility criteria for inclusion, search methods, data management, extracted information, risk of bias assessments, data analysis, subgroup analysis and sensitivity analysis. Next, results of the analysis are presented. General characteristics and risk of bias assessments of included studies are summarized, followed by results of the main analysis, subgroup analysis and sensitivity analysis for efficacy and safety outcomes. The findings are reviewed and interpreted in the context of relevant literature. Finally, strengths and limitations of the review are described.

Chapter 5: The final chapter contains concluding remarks and contextualization of the findings.

CHAPTER 2: BACKGROUND

2.1 POSTMENOPAUSAL OSTEOPOROSIS

Bone remodeling is the process by which old bone is replaced with new bone, occurring in five defined phases (8). In the activation phase, osteoclasts, giant multi-nucleated macrophage-like cells, are attracted chemically to the bone surface. In the resorption stage, osteoclasts produce an acidic environment to dissolve and remove a defined depth of bone from the surface. Subsequently during the reversal phase, osteoclasts undergo apoptosis and osteoblasts are recruited to the bone surface. They initiate the formation phase to deposit collagen that mineralizes to form new bone. In the quiescence or resting phase, bone tissue remains dormant, protected by osteoblasts until the next cycle of remodeling begins.

In premenopausal women, the rate of new bone formation is approximately equivalent to the rate of bone resorption. However, during menopause, a marked decrease in the estrogen hormone leads to an increase in osteoclastic activity without a corresponding increase in osteoblastic activity. Estrogen down-regulates factors that increase osteoclast production in the bone marrow. With a decline in estrogen and subsequent increase in osteoclast production, bone loss can occur rapidly. The average decrease in bone mineral density (BMD) is 10 percent during the transition from pre- to post-menopause (9). Calcium absorption also decreases with age, adding to the negative calcium balance in the body and increased fragility of the bone structure.

Although postmenopausal osteoporosis is the most prevalent form of osteoporosis, secondary osteoporosis can occur where bone loss is caused by an underlying illness such as rheumatoid arthritis, Crohn’s disease, hyperthyroidism, or diabetes mellitus. Osteoporosis can also occur in older men due to a reduction in testosterone. Risk factors for osteoporosis include a variety of genetic, nutrition and lifestyle factors. Women with a family history of osteoporosis, low estrogen levels, low body weight, menopause before 45 years of age, and those with low sunlight exposure, inadequate calcium and vitamin D consumption, excess alcohol intake, smoking habits, and prolonged immobility are at high risk of osteoporosis (10).

2.2 FRAGILITY FRACTURES

Osteoporosis is a silent disease of gradual bone loss until the occurrence of a fragility fracture. Fragility fractures are caused by low-energy trauma unlikely to fracture bones of normal density, such as a fall from standing height or less. These fractures are associated with significant pain, loss of independence, and decreased quality of life. The most common sites for bone fractures are the spine, hip and wrist. Spinal or vertebral fractures are the most common type of osteoporotic fracture, and may be asymptomatic (*i.e.,* radiographic or morphometric) or symptomatic (*i.e.,* clinical). Most vertebral fractures are morphometric and may be undetected except in examinations. Patients with more severe vertebral deformities tend to have chronic pain that leads to the diagnosis of clinical vertebral fractures (11, 12). Both asymptomatic and symptomatic vertebral fractures are strongly associated with an increased risk for future fractures. In the Study of Osteoporotic Fractures cohort, women who already sustained a fracture showed an approximate three-fold increase in risk of future vertebral fractures (13, 14). Non-vertebral fractures include fractures in all other regions except the spine. Trends in the temporal sequence of osteoporotic fractures indicated that the wrist is the first site to become vulnerable to fractures (15). In a cohort study of women referred to BMD examination, wrist fractures were the most common type of prevalent osteoporotic fracture (16). However, wrist fractures themselves are not associated with as high morbidity compared to fractures of the hip. Hip fractures occur at the proximal femur, are associated with the highest excess mortality for patients, and cost the most to repair. Published one-year mortality rates in patients who sustained a previous hip fracture treated in usual care ranged from 14% to 58% (17). In addition to loss of independence and quality of life for the patient, annual health-care costs of hip fractures are high. A study using cohort data approximated the annual direct attributable health-care costs in 2010 Canadian dollars for hip fractures in women was $282 million in Ontario and $1.1 billion in Canada (18). A study using administrative and community data found in 2010, 53% of the direct cost from acute care is associated with hip fractures, followed by wrist fractures accounting for 9% of total costs (19). The aggregate cost of osteoporotic fractures in Canada was estimated at 4.6 billion in 2011 for 130,000 fractures, which represented an 83% increase in cost since 2008 (20). The cost and prevalence of

osteoporosis is expected to increase in coming years. Globally, the population over age 60 is growing faster than all other age groups. The United Nations Population Division estimated in 2017 that the number of persons aged 60 and above is expected to double from 962 million to 2.1 billion by 2050. Sixty-five percent of the growth in population is expected to occur in Asia, with 11 percent occurring in the Latin America and the Caribbean. As of 2017, Europe has the highest percentage of people aged 60 and above (25%), followed by North America (22%), Oceania (17%), Asia, Latin America and the Caribbean (12%, respectively) (21). Thus, the burden of osteoporosis and related fragility fractures will rapidly increase worldwide.

2.3 DIAGNOSTIC CRITERIA

Osteoporosis can be diagnosed based on fracture history or the value of bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry. The World Health Organization (WHO) defined osteoporosis as those with BMD at the hip or lumbar spine that is 2.5 standard deviations (SD) or more below the average young adult peak bone mass (22). Peak bone mass (PBM) is the maximum amount of bone attained during adulthood, and is typically achieved by age 30 (23). BMD can be used to calculate a standardized T-score, which represents a comparison of the bone density versus a person of the same sex at 30 years of age, with results expressed in standard deviation units T-scores below -2.5 are indicative of osteoporosis (22). T-scores between -1.0 and -2.5 are classified as osteopenia or low bone mass, and normal adults are expected to have T-scores above -1.0.

Although BMD is commonly used for diagnosis of osteoporosis, several limitations are associated with its use as the main diagnostic criteria. Firstly, BMD results may vary depending on the site of measurement, the equipment used to measure bone density, and reference values used for comparison. Additionally, it is controversial whether low BMD is a good predictor of future fracture incidence, which is the single most clinically important consequence of osteoporosis. Hence, recent clinical guidelines recommend examining patients for additional risk factors for fragility fractures in addition to testing for BMD. Risk calculators such as FRAX (which calculates the 10-year probability

of a major osteoporotic fracture) are being used increasingly to provide a more comprehensive assessment of individual fracture risk (24).

Several pharmacologic interventions are available for the prevention of treatment of osteoporosis, one of the first-line medications being bisphosphonates. Other medications indicated for postmenopausal osteoporosis include vitamin D analogs, hormone replacement therapy (*e.g.,* estrogen and progestin), selective estrogen receptor modulators or SERMs (*e.g.,* raloxifene, bazedoxifene, lasofoxifene), denosumab, strontium ranelate, and parathyroid hormone analogue teriparatide. These interventions may affect the bone in similar (*i.e.,* hormone replacement therapy) or alternative mechanisms (*i.e.,* parathyroid hormone) to bisphosphonates. They have been hypothesized to work synergistically with bisphosphonates in certain subgroups of patients such as those with higher bone turnover to reduce the loss of bone mineral density (25); however, their effects on fracture prevention remain unclear.

2.4 BISPHOSPHONATES FOR POSTMENOPAUSAL OSTEOPOROSIS

Bisphosphonates are analogues of naturally occurring inorganic pyrophosphates chemically modified to resist metabolism by phosphatases (3). They contain a carbon atom joined by two phosphate groups, and have a high affinity for hydroxyapatite crystals in the bone. They are absorbed by osteoclasts mediating the resorption phase of bone remodeling. Once internalized, bisphosphonates inhibit osteoclast function and induce apoptosis, thereby suppressing bone turnover.

The affinity of a bisphosphonate for hydroxyapatite, and its potency to inhibit bone resorption, can be modified by changing the composition of the two lateral side chains. Non-nitrogen containing bisphosphonates (*e.g.,* clodronate, etidronate, tiludronate) are less potent compared to those containing nitrogen (*e.g.,* zoledroinc acid, alendronate, risedronate). Kinetic studies found the rank order of affinity was highest for zoledronic acid, followed by alendronate, ibandronate, and risedronate (26).

Bisphosphonates are first-line therapies for treatment and prevention of postmenopausal osteoporosis. Seven bisphosphonates were found to be approved in at least one country for postmenopausal osteoporosis based on a literature review of clinical guidelines (Table 2.1). The five most widely approved bisphosphonates are alendronate, risedronate, etidronate, ibandronate, and zoledronic acid. Minodronate is only approved in Japan, while clodronate is only approved in Italy. Three of the seven bisphosphonates are administered orally (alendronate, risedronate, etidronate). Ibandronate can be administered orally or intravenously. Zoledronic acid can be administered only intravenously. Clodronate can be administered either orally or intramuscularly. However, regions vary in which of the seven bisphosphonates are indicated for postmenopausal osteoporosis. For example, a cyclic etidronate regimen is approved in Canada for postmenopausal osteoporosis, but not in the United States or the United Kingdom. Ibandronate is not indicated for postmenopausal osteoporosis in Canada, but is approved in the United States, United Kingdom, and Italy.

Doses of bisphosphonates recommended for postmenopausal osteoporosis also differ by agency, and can vary depending on treatment or prevention. A list of approved dosages for postmenopausal osteoporosis is shown in Table 2.2 based recommendations from clinical guidelines published by healthcare agencies. In addition to postmenopausal osteoporosis, bisphosphonates are used as treatments for other bone diseases such as Paget's disease, metastatic bone disease, and osteogenesis imperfecta. Due to the variation in approved bisphosphonates in each region, bisphosphonates indicated for other bone diseases have been used off-label for postmenopausal osteoporosis, such as pamidronate, neridronate, and tiludronate.

Most clinical guidelines recommend oral bisphosphonates, most frequently alendronate and risedronate, as first-line therapies. However, patients with contraindications such as gastrointestinal disease and those at higher risk for fracture are recommended to receive intravenous zoledronic acid or ibandronate. Etidronate is typically not suggested as first-line therapy. The 2010 Canadian clinical practice guidelines for osteoporosis recommend postmenopausal women requiring treatment to use alendronate, risedronate or zoledronic acid for fracture prevention (7), while etidronate is only

for those intolerant of first-line therapies. In 2015, a Canadian clinical practice guideline was developed for fracture prevention among adults living in long-term care that recommended residents with high risk of facture to take alendronate and risedronate as first-line therapy, followed by zoledronic acid in those with difficulty taking oral medications (27). Etidronate was not recommended. The 2016 American Association of Clinical Endocrinologists also recommended alendronate and risedronate as first-line therapies, zoledronic acid for those unable to use oral therapy, and ibandronate for patients requiring spine-specific efficacy (28). In the United Kingdom, the 2017 National Institute for Health and Care Excellence (NICE) guidelines recommend alendronate, ibandronate and risedronate for fracture prevention and intravenous zoledronic acid or ibandronate for those with contraindications to oral medication or higher risk of fracture (29). Japanese clinical guidelines also recommended oral bisphosphonates as first-line medications, but additional recommendations varied depending on the specific site of fracture (30).

Among oral bisphosphonates, alendronate is the most frequently prescribed first-line oral bisphosphonates, and one of the earliest approved bisphosphonates. It has the highest market share for prescriptions of oral bisphosphonates dispensed from US outpatient retail pharmacy settings, accounting for 83% of all dispensed oral bisphosphonates in 2002 and 72% in 2012 (6). It is often recommended in clinical practice guidelines as one of the first osteoporosis treatments for postmenopausal women at risk of fracture (7). Hence, alendronate is also most frequently used as the standard of comparison in head-to-head comparisons of osteoporosis medications.

Table 2.1: Bisphosphonates approved for postmenopausal osteoporosis

	Canada	United States	United Kingdom	Japan	Italy
Alendronate	✓	✓	✓	✓	✓
Risedronate	✓	✓	✓	✓	✓
Etidronate	✓	X	X	✓	✓
Ibandronate	X	✓	✓	X	✓
Zoledronic acid	✓	✓	✓	X	✓
Minodronate	X	X	X	✓	X
Clodronate	X	X	X	X	✓

Table 2.2: Approved doses of bisphosphonates

	Approved doses (equivalent total doses)	Route of administration
Alendronate	5 mg/day (35 mg/wk), 10 mg/day (70 mg/wk)	Oral
Risedronate	2.5 mg/day, 5 mg/day (35 mg/wk, 150 mg/m)	Oral
Etidronate	200 mg/day, 400 mg/day	Oral
Ibandronate	2.5 mg/day, 5 mg/day (150 mg/m), 100 mg/m 1 mg/m (3 mg/3m)	Oral IV
Zoledronic acid	5 mg/year	IV
Minodronate	1 mg/day, 50 mg/4 wk	Oral
Clodronate	800 mg/day 100 mg/week	Oral IM

Abbreviations: wk=week, m=month, m=months, IV=intravenous, IM=intramuscular. Doses based on clinical guidelines from Canada, US, UK, Japan and Italy. *Typically administered as cyclic 90-day treatment cycle with 14 days of etidronate and 76 days of calcium carbonate.

2.5 EFFICACY OF BISPHOSPHONATES

Regulatory approval by the Food and Drug Administration (FDA) for treatment in postmenopausal osteoporosis requires a trial to have vertebral fractures as a primary endpoint and demonstration of a significant reduction in vertebral fracture incidence over three years compared to placebo (4). The emphasis was put on vertebral fractures because they are highly predictive of future osteoporotic fractures and less influenced by extrinsic factors such as falls (31). Surrogate outcomes such as bone mineral density are accepted as “bridging” studies for the approval of additional regimens of the same bisphosphonate such as weekly or monthly administrations.

Four large-scale registration trials have assessed the fracture prevention efficacy. The Fracture Intervention Trials (FIT I and II), Vertebral Efficacy with Risedronate Therapy (VERT) trial, the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE), and the Health Outcomes and Reduced Incidence with Zoledronic acid ONce Yearly Pivotal Fracture Trial (HORIZON-PFT) are registration trials for the approval of daily oral alendronate, risedronate, ibandronate and yearly intravenous zoledronic acid, respectively. Evidence from these randomized,

controlled trials (RCT) showed significant effect of the bisphosphonates for prevention of vertebral fractures, and additionally hip fractures for alendronate and zoledronic acid.

Three Cochrane reviews have assessed previously the fracture prevention efficacy of alendronate, risedronate, and etidronate, each compared to placebo (32-34). The pooled efficacy estimates were separated for primary and secondary prevention trials (Table 2.3, 2.4). Studies that included women whose bone density was within two SD of the mean or those with prevalence of vertebral fracture at baseline less than 20% were classified as primary prevention studies. Trials that included women with bone density more than two SD below the mean or those with prevalent vertebral fractures, or those with age greater than 62 years were classified as secondary prevention studies. The pooled estimates for relative risk indicate alendronate and risedronate are both more effective than placebo at reducing vertebral, non-vertebral and hip fractures among participants in secondary prevention trials, while etidronate is only significantly better at reducing vertebral fractures in the same population. For primary prevention studies, only alendronate is significantly better than placebo at reducing vertebral fractures only. No other treatments were found to be significantly better than placebo at reducing any other type of fracture.

Table 2.3: Results of Cochrane reviews for primary prevention studies (alendronate 10 mg/day, cyclic etidronate 400 mg/day, risedronate 5 mg/day)

Site of fracture	RR (95% CI)		
	Alendronate	**Etidronate**	**Risedronate**
Vertebral	**0.55 (0.38, 0.80)**	3.03 (0.32, 28.44)	0.97 (0.42, 2.25)
Non-vertebral	0.89 (0.76, 1.04)	0.56 (0.20, 1.61)	0.81 (0.25, 2.58)
Hip	0.79 (0.44, 1.44)	--	--
Wrist	1.19 (0.87, 1.62)	--	--

RR=relative risk, 95% CI=95% confidence interval. Bolded effect estimates are significantly better than placebo at preventing the fracture type. Dashed lines indicate insufficient studies to provide estimates (no primary prevention studies for hip and wrist in etidronate, 1 primary prevention study each for hip and wrist in risedronate).

Table 2.4: Results of Cochrane reviews for secondary prevention studies (alendronate 10 mg/day, cyclic etidronate 400 mg/day, risedronate 5 mg/day)

Site of fracture	RR (95% CI)		
	Alendronate	**Etidronate**	**Risedronate**
Vertebral	**0.55 (0.43, 0.69)**	**0.53 (0.32, 0.87)**	**0.61 (0.50, 0.76)**
Non-vertebral	**0.77 (0.64, 0.92)**	1.07 (0.72, 1.60)	**0.80 (0.72, 0.90)**
Hip	**0.47 (0.26, 0.85)**	1.20 (0.37, 3.88)	**0.74 (0.59, 0.94)**
Wrist	0.50 (0.34, 1.73)	0.87 (0.32, 2.36)	0.67 (0.42, 1.07)

RR=relative risk, 95% CI=95% confidence interval. Bolded effect estimates are significantly better than placebo at preventing the fracture type.

2.6 SAFETY CONCERNS AND LONG-TERM TREATMENT

The long half-lives of bisphosphonates enable them to remain in bone for a prolonged period, leading to safety concerns over long-term adverse events due to oversuppression of bone turnover. Reports of rare adverse events associated with prolonged bisphosphonate use surfaced regarding events such as osteonecrosis of the jaw, atypical femoral fracture and atrial fibrillation. Patient-individualized “drug holidays” have been recommended after three to ten years of treatment depending on level of fracture risk to reduce the accumulation of bisphosphonates in the body and potentially decrease the risk of rare adverse events (35).

Osteonecrosis of the jaw associated with bisphosphonate therapy was first reported in 2003 in patients with metastatic cancer receiving intravenous bisphosphonates (36). It is defined as an area of exposed bone in the maxillofacial region presenting at least 8 weeks. The condition is estimated to be extremely rare, occurring in 1/10,000 to 1/100,000 patient treatment years (37). The risk is especially high for patients with underlying malignancies, and in those taking bisphosphonates longer than three years (38). Atypical femoral fractures have been also associated with long-term bisphosphonate therapy in patients with prolonged alendronate treatment (39) and are distinguished from common femur fractures by radiographic characteristics such as a localized cortical thickening or “beaking” (40). Studies with and without radiographic confirmation of these fractures have indicated the absolute incidence of atypical femoral fractures are low, however an association appears to be present with bisphosphonates.

Results of the HORIZON trial suggested evidence of significantly higher rates ($p<0.001$) of atrial fibrillation requiring hospitalization among participants receiving zoledronic acid (1.3%) compared to those receiving placebo (0.5%) (4). However, the overall incidence of atrial fibrillation was similar among both groups. A population-based case-control study among women in a clinical setting found a significant association between ever users of alendronate and odds of atrial fibrillation (41). However, post-hoc studies of alendronate (42) and risedronate (43) did not show statistically significant increased risk of atrial fibrillation.

Adverse events related to routes of bisphosphonate administration are also of concern because of their association with low patient compliance, which decreases the effect of treatment. Although oral daily bisphosphonates were found to be effective in clinical trials, low compliance in patient populations were found, in part due to a range of moderate to severe gastrointestinal-related side effects including nausea, vomiting, esophageal ulcers, stricture, perforation and bleeding. A retrospective cohort study among 75, 593 women found those who experienced gastrointestinal adverse events were 29% less likely to adhere to the treatment regimen compared to those who did not (44). Acute phase responses are found in approximately 18% of patients with intravenous administration of bisphosphonates, encompassing a range of flu-like symptoms such as fever, headache, myalgia, and arthralgia that typically occur within 24 hours to 3 days after infusions (45).

2.7 RATIONALE FOR CONDUCTING A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Due to the lack of large-scale, head-to-head, randomized, controlled trials comparing different bisphosphonates, indirect comparison methods can be used to fill in the gaps and contribute to the body of evidence. Network meta-analysis (NMA) extend the concept of traditional meta-analysis by incorporating indirect as well as direct comparisons between studies with common comparators. NMA provides pooled effect estimates for any pair of treatments within a connected network for an outcome of interest. Due to its ability to estimate relative rankings and summarize effects between combinations of different treatments, NMAs have been increasingly used in health-care decision making. In addition, Bayesian NMA methods offer the advantage of interpretation of the pooled effect as a probability, thus the results facilitate interpretation and knowledge dissemination.

Twelve network meta-analyses have been previously conducted, and a summary of the studies, interventions, comparators, outcomes and analysis are listed in Table 2.5. Most of the NMAs were run using the Bayesian framework, and the publication years ranged from 2009 to 2017. All NMAs included RCTs of postmenopausal women with osteoporosis, and four also included men with

osteoporosis (46-49). Four NMAs used treatment duration less than one or three years as an exclusion criterion (47, 50-53) and five NMAs stated they did not include studies that did not report fracture outcomes (46, 47, 49, 53, 54). The NMAs have a range of included studies, interventions and outcomes. However, no NMA assessed combination treatments of bisphosphonates or health-related quality of life. Only one network meta-analysis assessed minodronate (49), two included clodronate (49, 55), and six did not evaluate etidronate (46, 47, 51, 56, 57). Two studies included an assessment of safety outcomes; however, both NMAs examined safety as “any adverse events” broadly without further differentiation. Both network meta-analyses also excluded etidronate (55, 56) and one also excluded ibandronate (55). Additionally, two network meta-analyses differentiated between radiographic and clinical vertebral fractures (50, 53), while six of the networks did not include wrist fracture (46, 51, 53, 56, 57).

To build on existing evidence base in literature, a comprehensive bisphosphonate network meta-analysis incorporating both efficacy and safety outcomes is required. Interventions of newer bisphosphonates (*e.g.,* minodronate and clodronate) and off-label bisphosphonates (*e.g.,* pamidronate, neridronate, tiludronate) may be compared to the five most widely prescribed bisphosphonates to gain information on the efficacy of all potentially available treatments. Combination treatments of bisphosphonates with other anti-osteoporotic treatments should be included as they are important for assessing potential synergistic interactions between osteoporosis treatments. Patient-reported outcomes such as quality of life are expected to become more frequently evaluated in osteoporosis as it is a chronic disease and fractures are associated with significant decreases in quality of life. Safety outcomes such as serious adverse events, withdrawal due to adverse event, gastrointestinal adverse events and acute phase response can provide additional information on the holistic impact of bisphosphonate treatments on patients. In addition to a network meta-analysis evaluating both direct and indirect comparisons, an independent systematic review and meta-analysis on alendronate versus other comparators will be undertaken to evaluate the pooled effect estimates provided by direct comparisons in the literature.

Table 2.5: Previously conducted network meta-analyses

Author	Included studies	Interventions	Comparators	Efficacy outcomes	Safety outcomes	Analysis (software)
Liu 2017	RCTs of postmenopausal osteoporosis (BMD T-score ≤2.5, or ≤1.5 with fracture).	ALE, RIS, IBA, ZOL; STR, BAZ, RAL, LAS, CT	Any included intervention or placebo	Vertebral, non-vertebral, LS BMD, FN BMD, TH BMD	Any adverse events	Bayesian NMA; RE (WinBUGS)
Sanderson 2016	RCTs in men and women that reported fracture outcomes and/or BMD	ALE, IBA, RIS, ZOL	Any included intervention, placebo/non-active comparators	Vertebral, non-vertebral, hip, wrist, proximal humerus, other sites, FN BMD	None	Bayesian NMA (WinBUGS)
Yang 2016	RCT of women with postmenopausal osteoporosis and study size ≥ 30 patients	ALE, ETI, RIS, ZOL, CLO; DEN, RAL, STR, TER, EST+PRO	Any included intervention or placebo	Non-vertebral, hip, wrist	Any adverse event	Bayesian NMA; RE
Zhou 2016	RCTs in men and women with primary osteoporosis that reported fracture outcomes	ALE, ETI, RIS, IBA, ZOL, CLO, MIN, NER, PAM, TIL, OLP	Any included intervention or placebo	Radiographic vertebral fracture, non-vertebral, hip, wrist, any fracture	None	Frequentist NMA; RE (STATA)
Ellis 2014	RCTs of postmenopausal women with primary osteoporosis	ALE, IBA, RIS; BAZ	Any included intervention or placebo	Non-vertebral fractures	None	Bayesian NMA (WinBUGS)
Tadrous 2013	RCTs in men and women with primary osteoporosis	ALE, ETI, RIS, ZOL	Any included intervention or placebo	None	Any GI-related AE, esophageal AE, nausea, serious upper GI, WDAE	Bayesian NMA; RE (WinBUGS)
Freemantle 2013	RCTs of postmenopausal women with ≥ 1 year treatment, ≥ 10 patients/arm	ALE, RIS, ETI, IBA, ZOL; STR, TER, RAL	Any included intervention or placebo	Radiographic vertebral, clinical vertebral, non-vertebral, hip, wrist	None	Bayesian NMA (WinBUGS)
Migliore 2013	RCTs of women with postmenopausal osteoporosis and vertebral fracture as primary / secondary outcome, ≥ 3 years treatment	ALE, RIS, IBA, ZOL; DEN	Any included intervention or placebo	Morphometric vertebral, clinical vertebral	None	Bayesian MTC (WinBUGS)
Murad 2012	RCTs of men and women with osteoporosis that report fracture outcomes	ALE, RIS, IBA, ZOL TER, RAL, BAZ, DEN, CAL, VID.	Any included intervention or placebo	Vertebral, non-vertebral, hip	None	Bayesian NMA; RE (WinBUGS)
Hopkins 2011	RCTs of postmenopausal women with osteoporosis that reports fractures as primary or secondary outcomes	ALE, RIS, ETI, IBA, ZOL DEN, RAL, TER, STR	Any included intervention or placebo	Vertebral, non-vertebral, hip, wrist	None	Bayesian ITC; RE (WinBUGS)
Jansen 2011	RCTs in postmenopausal women with osteoporosis, followup ≥ 3 years	ALE, ETI, IBA, RIS, ZOL	Any included intervention or placebo	Morphometric vertebral, hip, non-vertebral-nonhip.	None	Bayesian NMA; FE (WinBUGS)
Jansen 2009	RCTs in postmenopausal women with osteoporosis, treatment ≥ 3 years.	ALE, RIS, IBA, ZOL	Any included intervention or placebo	Morphometric vertebral	None	Bayesian NMA, FE/RE (WinBUGS)

Abbreviations: RCT=randomized controlled trial, LS=lumbar spine, FN=femoral neck, TH=total hip, NMA=network meta-analysis, RE=random-effects model, FE=fixed-effects model ALE=alendronate, RIS=risedronate, ETI=etidronate, IBA=ibandronate, ZOL=zoledronic acid, CLO=clodronate, MIN=minodronate, NER=neridronate, TIL=tiludronate, PAM=pamidronate, OLP=olpadronate. STR=strontium, BAZ=bazedoxifene, RAL=raloxifene, LAS=lasofoxifene, CT=calcitonin, DEN=denosumab, EST+PRO=estrogen and progestin, CAL=calcium, VID=vitamin D.

CHAPTER 3: SYSTEMATIC REVIEW AND META-ANALYSIS OF ALENDRONATE

3.1 INTRODUCTION

Systematic reviews follow a set of systematic, transparent, reproducible and pre-defined steps, including a focused research question, comprehensive search strategy, uniformly applied inclusion criteria, and rigorous critical appraisal, to assemble a pool of evidence to address the research hypothesis (58). A systematic methodology aims to reduce bias in the selection and extraction of evidence. A meta-analysis provides a quantitative synthesis of the systematically collected data from the review. The following review and meta-analysis were conducted following the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (59) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (60).

3.2 METHODS

3.2.1 ELIGIBILITY CRITERIA

Selection criteria are summarized in Table 3.1. Studies that enrolled postmenopausal women were included. Studies that enrolled both men and women but reported results separately by sex and trials that comprised of at least 95% postmenopausal women were also included to provide the maximum evidence base for answering the research question. However, trials that enrolled exclusively males, premenopausal women or those with secondary osteoporosis were excluded. The intervention of interest is alendronate administered a dosage approved by a regulatory agency. Oral administrations of 5 mg daily or 35 mg weekly for the prevention of osteoporosis and 10 mg daily or 70 mg weekly for the treatment of osteoporosis were included. The doses of 5 mg daily and 10 mg daily were kept separate in the analysis due to differences between their intended use (*i.e.,* prevention versus treatment). However, varying administration frequencies of the same total dose (*e.g.,* 5 mg daily versus 35 mg weekly) were combined to increase analysis power based on studies that demonstrated their therapeutic equivalence (61, 62). The main comparator is placebo which included groups that received no treatment, matching placebo, or background supplementation with

calcium and/or vitamin D at a dosage that is equally administered to all treatment arms. Additional comparisons to other bisphosphonates or non-bisphosphonates (*e.g.,* SERMs, teriparatide, strontium ranelate) were also included. Efficacy outcomes comprised of vertebral fractures (classified into radiographic or clinical vertebral fractures), non-vertebral fractures, wrist fractures, hip fractures, and quality of life. Safety outcomes comprised of withdrawal due to adverse events, serious adverse events, and four specific adverse events of interest: gastrointestinal adverse events, atypical femoral fracture, atrial fibrillation, and osteonecrosis of the jaw. Eligible studies were randomized, controlled trials with at least one year of treatment duration. The threshold of at least one year duration was chosen to allow sufficient followup time to observe the effects of alendronate on fractures in all sites, since non-vertebral fractures occur at a lower rate compared to other fractures (5). Additionally, the threshold is also clinically important, because the Canadian clinical practice guidelines recommend one year as the minimum amount of time before patients commencing bisphosphonate therapy should be re-assessed for fracture risk (7).

Reports and abstracts from all languages and countries were eligible. A study examining the impact of including grey literature in 135 meta-analyses of randomized controlled trials in various clinical areas found that on average, published works resulted in 15% larger estimates of intervention effect compared to the intervention effect including grey literature (63). This may be due to publication bias where studies with positive results are more likely to be published than trials showing null or negative results, thus leading to an exaggerated treatment effect (64). Although data from grey literature may be less rigorous due to lacking the peer-review stage mandatory for published data and the search methods may be less reproducible due to the lack of structure in searching grey literature databases, we decided to include grey literature to broaden the scope of evidence, to reduce the risk of publication bias and to potentially increase the validity of resulting effect estimates.

Table 3.1: Summary of selection criteria for systematic review

	Inclusion criteria	Exclusion criteria
Population	Postmenopausal women	Premenopausal women, secondary osteoporosis, men (> 5% of population)
Intervention	Alendronate doses at 5 mg/day, 10 mg/day, 35 mg/week, 70 mg/week, alone or combined with other active treatments	
Comparator	Placebo (no treatment, calcium and/or vitamin D), other active treatments	
Outcomes	*Efficacy* Vertebral fractures (radiographic) Vertebral fractures (clinical) Non-vertebral fractures Hip fractures Wrist fractures Health-related quality of life *Safety* Withdrawal due to adverse events Serious adverse events Gastrointestinal adverse events Osteonecrosis of the jaw Atypical femoral fracture Atrial fibrillation	Studies assessing surrogate endpoints (*e.g.,* bone mineral density, bone turnover markers, bone microarchitecture) that provide no fracture data are excluded from analysis
Study designs	Randomized controlled trials with ≥ 1 year treatment, conference abstracts	Non-randomized trials (*e.g.,* single arm extension, observational study), less than 1 year treatment
Other	Any language, country, published and unpublished data (FDA, EMA, Health Canada drug approval reports, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform)	

3.2.2 SEARCH METHODS

The previous Cochrane review conducted in 2008 focused on alendronate 5 mg and 10 mg daily compared to placebo, and did not include head-to-head comparisons of alendronate versus other active treatments (32). In order to address this issue and to provide greater insight on the availability of head-to-head trials in literature, a search update was conducted internally in 2012 that re-ran the original search strategy from the 2008 Cochrane review from database inception to June 28, 2012. It intended to capture any excluded head-to-head trials of alendronate from the previous Cochrane review. In the process, the review authors screened all resulting abstracts, re-assessing abstracts that were included in the 2008 Cochrane review in addition to any new records. Studies that met the

PICOs criteria, which was identical to the 2008 Cochrane review with the exception of including head-to-head comparisons, were eligible for the analysis. In the current update, we built on the work conducted in the 2012 update by assessing the full-text studies found from the previous search. An experienced medical information specialist then updated the search strategy from June 28, 2012 to August 26, 2017 with a 6 month overlap (*i.e.,* from December 1, 2011) in order to ensure that all relevant articles within the expected timeframe are captured. Searches of the following databases were conducted, all on the Ovid platform: Embase Classic + Embase, Ovid MEDLINE (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations), and the Cochrane Central Register of Controlled Trials. Search strategies used a combination of controlled vocabulary and keywords adjusted across databases with no restrictions placed on language or date of publication. The full search strategies are in Appendix 1. Grey literature searches of the databases ClinicalTrials.gov and the ICTRP Search Portal were performed on December 5, 2017, using the terms for each bisphosphonate. Studies retrieved from the clinical trial record databases were accessed at later dates for additional information. Drug approval documents and medical reviews developed by the United States Food and Drug Administration, European Medicines Agency, and Health Canada were initially searched for extractable information on December 16, 2017.

3.2.3 STUDY RECORDS AND DATA MANAGEMENT

All retrieved records from the systematic literature search were stored a RIS file which entered a citation manager (Endnote X7, Clarivate Analytics) for de-duplication. Study records were first automatically de-duplicated in EndNote, and manually de-duplicated by two reviewers afterwards. Records were uploaded in bulk to a systematic review software (DistillerSR, Evidence Partners Inc.), where the screening of abstracts, full-texts, extraction of data and risk of assessments took place. Screening, data abstraction and risk of bias forms were created and piloted before study selection began. Extracted data were verified in DistillerSR and exported in the format of a Microsoft Excel file for analysis.

Multiple reports of the same trial from published and unpublished sources were linked to prevent redundant outcome extraction. At full-text screening, trial name, clinical trial registry identification, and references to previously published reports of the same trial were collected. This information was compiled to identify and group multiple published or unpublished records of the same trial. Outcomes included in each individual report were compared and assessed for data extraction, and the study with the most extractable outcomes is considered the principle study. Risk of bias assessments and all subsequent data extraction from other reports of the same trial were extracted on the principle study record. In the event of multiple reporting of the same outcome within the same trial, the most recent, adjudicated report of the outcome was extracted.

3.2.4 STUDY SELECTION

Study abstracts were screened in duplicate by two trained and independent reviewers for inclusion based on the eligibility criteria. Full-texts of potentially relevant abstracts were retrieved and uploaded into DistillerSR for the next round of screening. If there was uncertainty regarding eligibility of the study based on the abstract alone, the record would be included for full-text screening. Where it was likely that the record was an abstract (*e.g.,* conference name clearly stated, single page, page numbers accompanied by letters), it was screened as a full-text based on the available information for inclusion. Any discrepancy marked by the software was discussed between reviewers until consensus was reached. If a consensus could not be reached, the issue was discussed with a third reviewer. Reviewers were not blinded regarding study authors or location.

3.2.5 DATA EXTRACTION

Information was extracted regarding the publication (*e.g.,* author, year of publication, trial name, clinical registry number, published protocol, linked companion studies), study design, (*e.g.,* primary study outcome, inclusion and exclusion criteria), and participant characteristics (*e.g.,* calcium and/or vitamin D supplementation, prior treatment experience, sample size, age, mean lumbar spine T-

score, and participants with baseline vertebral fractures). For each intervention group, we recorded the dose, frequency, and route of administration. Outcome data included definitions of the outcomes provided by the study authors, duration of treatment, and analysis population (*e.g.,* intent-to-treat, modified intent-to-treat, per protocol, or safety). Data for study characteristics, participants characteristics and outcomes were extracted by one reviewer using standardized abstraction forms in DistillerSR and subsequently verified by a second reviewer. Any discrepancy found by the second reviewer relating to the accuracy of data extracted by the first reviewer was resolved through discussion with both reviewers, and if necessary, with a third reviewer. A study by Buscemi et al. (2006) compared the accuracy of data extracted by a single reviewer with verification by a second reviewer to double independent data abstraction by two reviewers a systematic review assessing melatonin for the management of sleep disorders (65). They found that a statistically significant greater number of errors occurred in single data extraction with verification (78 errors *vs* 51 errors; p=0.007). However, double independent extraction took 49.0 minutes longer per article which translated to a statistically significant increase from single data extraction with verification (p=0.003). Additionally, it was observed that inaccuracy in single data extraction with verification did not translate to a substantial difference in the resulting effect estimates in terms of "direction, magnitude, precision or significance of pooled estimates for most outcomes". We used single data extraction with verification primarily to decrease the associated time cost due to anticipating a high volume of studies. However, we also tried to set up measures to reduce inaccuracy and bias associated with single data extraction with verification. Both reviewers were extensively trained prior to data extraction through collaboratively developing the data abstraction form, standardizing definitions for data extraction items, and researching literature in order to gain familiarity with the subject domain.

For dichotomous outcomes, we recorded the number of people with events, total randomized participants and total participants included in the analysis. For quality of life, we recorded the total number of randomized and analyzed participants, baseline values, end of trial measurements, and the change from baseline if available. A vertebral fracture was considered radiographic if the study authors defined the fracture as "asymptomatic", "radiographic", "morphometric", or referenced a

quantitative or semi-quantitative assessment. If the vertebral fracture was reported as “clinical”, “symptomatic”, or as an adverse event, it was classified as a clinical vertebral fracture. Non-vertebral, hip and wrist fractures were extracted as defined by the authors. In the case of unclear definitions, femoral neck fractures were inferred as hip fractures and distal radius or Colles’ fractures were inferred as wrist fractures. The unit of measurement was the number of people with fractures. Health-related quality of life was extracted as a total score regardless of the outcome measure. Safety outcomes were recorded as defined by the study authors. Withdrawal due to adverse events was extracted as the number of participants who discontinued from the study.

3.2.6 RISK OF BIAS IN INIDIVIDUAL STUDIES

Risk of bias was assessed by two reviewers using the Cochrane Collaboration’s domain-based risk of bias tool for RCTs (59). Seven domains of bias representing five types of bias were assessed: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. In addition, two domains were assessed separately for subjective/objective outcomes and efficacy/safety events. Disagreements on risk of bias were resolved by discussion.

Blinding was evaluated separately for subjective and objective outcomes as recommended in the Cochrane Handbook because subjective outcomes in unblinded studies may be prone to greater risk of bias than objective outcomes (59, 66). Although objective outcomes may include a degree of subjectivity, they tend to be less person-based and places greater emphasis on standardized criteria or equipment output. Objective outcomes include all fractures, jaw osteonecrosis, atrial fibrillation, and atypical femoral fracture. Subjective outcomes are quality of life, withdrawals due to adverse events, serious and gastrointestinal adverse events. Evaluation of incomplete outcome data was separated for efficacy and safety outcomes since analysis populations may differ. In judging risk of attrition bias, we first examined the end-of-trial followup. If it included at least 80% of randomized

participants, the study is likely at low risk of bias. The threshold of at least 80% of randomized participants completing followup was based on the system developed for the grading of evidence in *Evidence-Based Rheumatology* (67). Trials that lost more than 20% of randomized participants were considered to be at high risk of attrition bias which may lead to reduced study power and differential loss of participants where those that are remained in the trial are more or less likely to have the outcome of interest compared to those who left the trial (68). As a result, effect estimates from the analysis will be inaccurate and validity of the network meta-analysis will be impacted. However, attrition bias can occur even with greater than 80% followup rates if the withdrawal rates are significantly differential and participants are not missing at random (69). Therefore, in trials with greater than 80% followup, we assessed attrition bias additionally by comparing withdrawal rates and the reasons for discontinuation across all treatment groups. If possible, we assessed whether the causes may be related to the outcome (*i.e.,* if the reason for withdrawal may be due to sustaining a fracture or adverse event, or if the reason is unlikely to be related to the outcome of interest). For studies that had less than 80% followup, we also assessed whether they used appropriate methods for dealing with missing data (*i.e.,* multiple imputation as opposed to last observation carried forward), and if the analysis population was representative of randomized participants (*i.e.,* intent-to-treat as opposed to per-protocol analysis). A combination of factors including a threshold for followup completion and comparisons of withdrawal rates across treatment groups were used to assess the likelihood of attrition bias due to incomplete outcome data for efficacy and safety outcomes.

3.2.7 DATA ANALYSIS

Studies eligible for analysis were assessed qualitatively for clinical heterogeneity to determine if the participants, intervention and outcome characteristics are sufficiently alike to allow meaningful interpretation of the pooled results. Meta-analyses were undertaken using the software Review Manager (RevMan 5.3, The Cochrane Collaboration) with formal tests of interaction conducted for subgroup analyses. A descriptive summary will be provided where a meta-analysis is not possible.

A random-effects model assumes that included studies provide a random sample of estimates from a distribution of effects and we are intending to estimate the mean effect of this distribution. The fixed-effect model assumes all studies are estimating one true effect size, and the variability between observed effects of each study is due to sampling error. The random-effects model was chosen for all analyses because it is more conservative (70). It allows for not only sampling error but also between-study variability due to anticipated heterogeneity among clinical and methodological aspects of different trials (*e.g.,* varying patient populations, doses of drug, follow-up lengths). For binary outcomes (*e.g.,* fractures and safety adverse events), effect estimates are expressed as relative risk (RR) with 95% confidence intervals (95% CI). For continuous outcomes (*e.g.,* quality of life), measures will be converted to a standardized mean difference and a pooled estimate will be provided with 95% CIs. Results will be presented in forest plots, and the I^2 statistic will be shown as a measure of the percentage of variability in treatment effects due to between-study heterogeneity rather than chance. An I^2 greater than 50% indicates substantial levels of heterogeneity (59).

3.2.8 SUBGROUP ANALYSES

Subgroup analyses were decided *a priori* based on characteristics in subsets of patients or studies that may have varying impacts on estimates of treatment effect. We conducted three subgroup analyses:

i) *Secondary versus primary prevention trials:* It was hypothesized that patients with established osteoporosis and greater disease severity (*e.g.,* bone mineral density at least two standard deviations below the reference value or with prevalent vertebral fractures) may vary in treatment response compared to patients with osteopenia. Hierarchical criteria were established in previous reviews (32-34) to distinguish between secondary prevention trials with more severe osteoporosis patients and primary prevention studies with osteopenia participants.

ii) *Prior bisphosphonate experience:* The terminal elimination half-life of alendronate is approximately 10.5 years (71) and effects on bone density were observed up to seven years after treatment withdrawal (72). It was hypothesized that participants previously treated with alendronate may vary in response to bisphosphonate therapy when compared to bisphosphonate-participants due to potential residual effects. Thus, a subgroup analysis was conducted where studies enrolling exclusively participants with prior bisphosphonate experience were compared against trials comprising solely of participants who have not been previously treated with bisphosphonates. Prior bisphosphonate experiences of participants in a trial were determined based on specifications in the inclusion and exclusion criteria.

iii) *Treatment durations:* Although the base case taken for review analysis utilizes the longest time point, it was hypothesized that the duration of treatment with alendronate may affect the antifracture efficacy of alendronate therapy. Thus, subgroup analyses were conducted for one up to five years, depending on the availability of data.

Classification criteria for primary and secondary prevention trials

Studies were separated into primary and secondary fracture prevention trials, as defined in the Cochrane review based on a hierarchical classification (32-34). A study is classified as secondary fracture prevention if the trial limited inclusion to postmenopausal women whose bone mineral density was at least 2 standard deviations below the reference mean value among healthy, 30-year old women, or if all participants must have previously experienced a vertebral fracture. If inclusion criteria were unclear, baseline values were examined. A study was classified as primary prevention if the baseline mean T-score and SD were smaller than two, indicating the values are within two SD of the mean reference value, or if the prevalence of baseline vertebral fractures was less than 20%. In the case of unclear inclusion and baseline information, a trial was considered secondary prevention if the average age was above 62 years.

3.2.9 SENSITIVITY ANALYSES

Sensitivity analyses were performed on efficacy outcomes to test the robustness of findings in relation to assumptions made in the meta-analysis. We examined differences between effect estimates of the main analysis and four sensitivity analyses.

i) *Low risk of bias:* Studies with low risk of bias in the domain of incomplete data for efficacy outcomes were analyzed separately because these studies are expected to be of higher quality, having over 80% followup of all randomized participants at the end of trial time point.

ii) *Fracture as efficacy outcome:* Studies with fracture as an efficacy outcome were analyzed to assess whether there are differences in reporting quality between trials designed to examine fracture outcomes versus those that were not powered to assess fracture outcomes and only reported them as adverse events. Studies with fracture as efficacy outcomes are hypothesized to have higher quality reporting of related statistical methods and may describe in greater detail the assessment criteria and locations of fracture incidences. This may impact the resulting effect estimates from analysis.

iii) *Re-classification of primary and secondary prevention studies:* A threshold of two standard deviations below the reference value for bone mineral density and T-score was adopted from previous reviews to classify primary and secondary prevention studies. However, the WHO criteria for osteoporosis defined those with the disease as having BMD at least 2.5 SD below the reference mean, or a T-score lower than -2.5 (22). Thus, a sensitivity analysis using the threshold of 2.5 SD to classify primary and secondary prevention studies was performed to assess whether a shift in criteria would impact effect estimates from subgroup analyses.

iv) *Randomized versus analysis denominators:* A sensitivity analysis was planned for randomized versus analysis denominators because some end-of-study data were extracted based on a smaller population than all randomized participants (*e.g.,* those

with radiographs available for assessment for vertebral fractures). The extent of its impact on the effect estimates was investigated.

Table 3.2: Summary of subgroup and sensitivity analyses for systematic review

Subgroup analysis			
i)	Primary versus secondary prevention studies		
ii)	Studies with bisphosphonate-naïve patients versus studies with bisphosphonate-experienced patients		
iii)	Treatment durations of one to five years		
Sensitivity analysis		**Main analysis**	
i)	Studies with low risk of bias	i)	Studies with any level of bias
ii)	Studies with fracture efficacy outcome	ii)	Studies reporting fractures in any form
iii)	Primary prevention: BMD/T-score at most 2.5 SD below mean Secondary prevention: BMD/T-score at least 2.5 SD below mean	iii)	Primary prevention: BMD/T-score at most 2 SD below mean Secondary prevention: BMD/T-score at least 2 SD below mean
iv)	Denominator as number randomized	iv)	Denominator as number in analysis

3.2.10 PUBLICATION BIAS

Publication bias occurs when studies with significant results have a higher chance of publication than studies with non-significant results, and this will likely bias the resulting pooled estimates toward an inflated treatment effect. Funnel plots were used to assess the potential for publication bias in meta-analyses that included at least 10 studies. The standard error of each effect estimate was plotted vertically against the effect estimate on the horizontal axis. The vertical axis for standard error or sample size is inverted, with zero at the highest vertical end. Larger studies with greater sample size tend to have smaller standard error and higher precision, and will likely be plotted higher on the vertical axis. Smaller studies with fewer participants have larger standard error and lower precision, and are lower on the vertical axis. Treatment effects will be plotted on a logarithmic scale to ensure that effect estimates of the same magnitude but in opposite directions are equidistant from the null threshold. In the absence of publication bias, the funnel plot would be expected to have greater scatter at the bottom (due to larger effect of chance in the effect estimates of smaller studies with lower precision), and the shape will resemble a symmetric, inverted funnel. The presence of asymmetry is expected to look like gaps in the funnel plot of effect estimates, with more pronounced

asymmetry more likely to indicate the potential for substantial bias. However, publication bias may be only one of the causes of possible asymmetry found in funnel plots, with other possible explanations including lower methodological quality of smaller studies showing exaggerated treatment effects (73).

3.2.11 SUMMARY OF FINDINGS TABLES

In line with the previous Cochrane review on alendronate, a Summary of Findings (SoF) table will be provided. The SoF table presents analysis results for the seven most clinically important outcomes, while providing a rationale for judgements on the certainty of the evidence upon which the results are based. The overall quality of evidence is assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach developed by the GRADE Working Group, comprising of five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (74). The assessment of the quality of evidence in each domain followed the approaches detailed in Chapter 12 of the Cochrane Handbook (59). Each outcome is evaluated for limitations regarding each domain ranging from not serious to very serious, with each limitation causing a “downgrade” in the overall quality of evidence. The overall judgements range from very low quality where the authors are very uncertain about the resulting estimate, to high quality where further research is unlikely to change the confidence of the authors in the estimate of effect (59). The rationale for each “downgrade” in certainty is provided in the footnotes for each outcome. The SoF table was constructed using the GradePRO software (McMaster University, Evidence Prime Inc).

3.3 RESULTS

3.3.1 CHARACTERISTICS OF STUDIES

A total of 1,397 records were found in the search, and after duplicate removal 1,315 records were screened. Of the 330 full-texts assessed for eligibility, 103 records originated from the original Cochrane review in 2008 (32) or from an internal update of the review in 2012 (grey box in PRISMA

flow diagram, Figure 3.1). A total of 60 RCTs and 10 records with additional data to the main report were included in the qualitative analysis (Table 3.3), where 37 of the included RCTs originated from the Cochrane review and update. All included study records in the systematic review are listed in Appendix 3, and excluded full-text records are listed in Appendix 4.

No new studies were found among the grey literature, but two registry records in the WHO-ICTRP database provided fracture data as adverse events that allowed the inclusion of two previously excluded studies (75, 76). No additional studies were found from any regulatory agency reports; however, additional information was provided by three FDA reports (77-79) for three studies already included in the review (80-82). Generally, the dates of publication ranged from 1995 to 2016, and treatment durations ranged from 48 weeks to four years. Fifty-two studies enrolled women with established osteoporosis and were classified as secondary prevention trials, and only eight studies were primary prevention. Two trials included male participants (83, 84) that comprised of less than five percent of the total population. The mean age of participants ranged from 64.0 to 76.6 years, average T-scores of participants ranged from -1.3 to -3.9, and study sizes ranged from 32 participants to 4432 participants. Only one study reported four-year data (85), and one trial provided five-year data (86). Thirty-three studies from the previously conducted Cochrane review on alendronate were also included in the updated systematic review. Among included studies are the Fracture Intervention Trials (FIT I and II), two large scale studies of three and four years conducted on the antifracture efficacy of alendronate. Both examined alendronate compared to placebo, however only participants with vertebral fractures were enrolled in the Vertebral Deformity Study or FIT I (86). Participants without prevalent vertebral fractures at baseline were enrolled in the Clinical Fractures Study or FIT II (85). Participants who received alendronate in any of the two trials and completed treatment were eligible for inclusion in the FLEX study, a five-year extension study that examined the long-term efficacy of alendronate compared to discontinuing the bisphosphonate (87).

Two studies met the criteria for inclusion but were not included in analyses because all trial arms contained therapeutically equivalent doses which were pooled in analysis to increase power (*e.g.,* alendronate 5 mg/day and 35 mg/week) (61, 62).

Dose modifications during the study were accounted for during data analysis if the study reported the point in time at which the change in occurred. Three studies increased the alendronate dose from 5 mg/day to 10 mg/day, including both Fracture Intervention Trials where the dosage increased at two years of treatment in a three-year (86) or four-year trial (85), and a study where the dose was escalated after 18 months of a 30-month trial (88). Two studies reduced the dose of alendronate from 20 mg/day to placebo. One of these studies modified the dosage at one year of treatment in a two-year trial (89), and the other changed the dose at two years of a three-year trial (82). An additional study decreased the dose of alendronate from 20 mg/day to 5 mg/day after two years of treatment in a three-year trial (90). All dose modifications were described as protocol amendments due to the availability of newly published safety or efficacy results from other randomized, controlled trials.

Figure 3.1: PRISMA flow diagram for systematic review

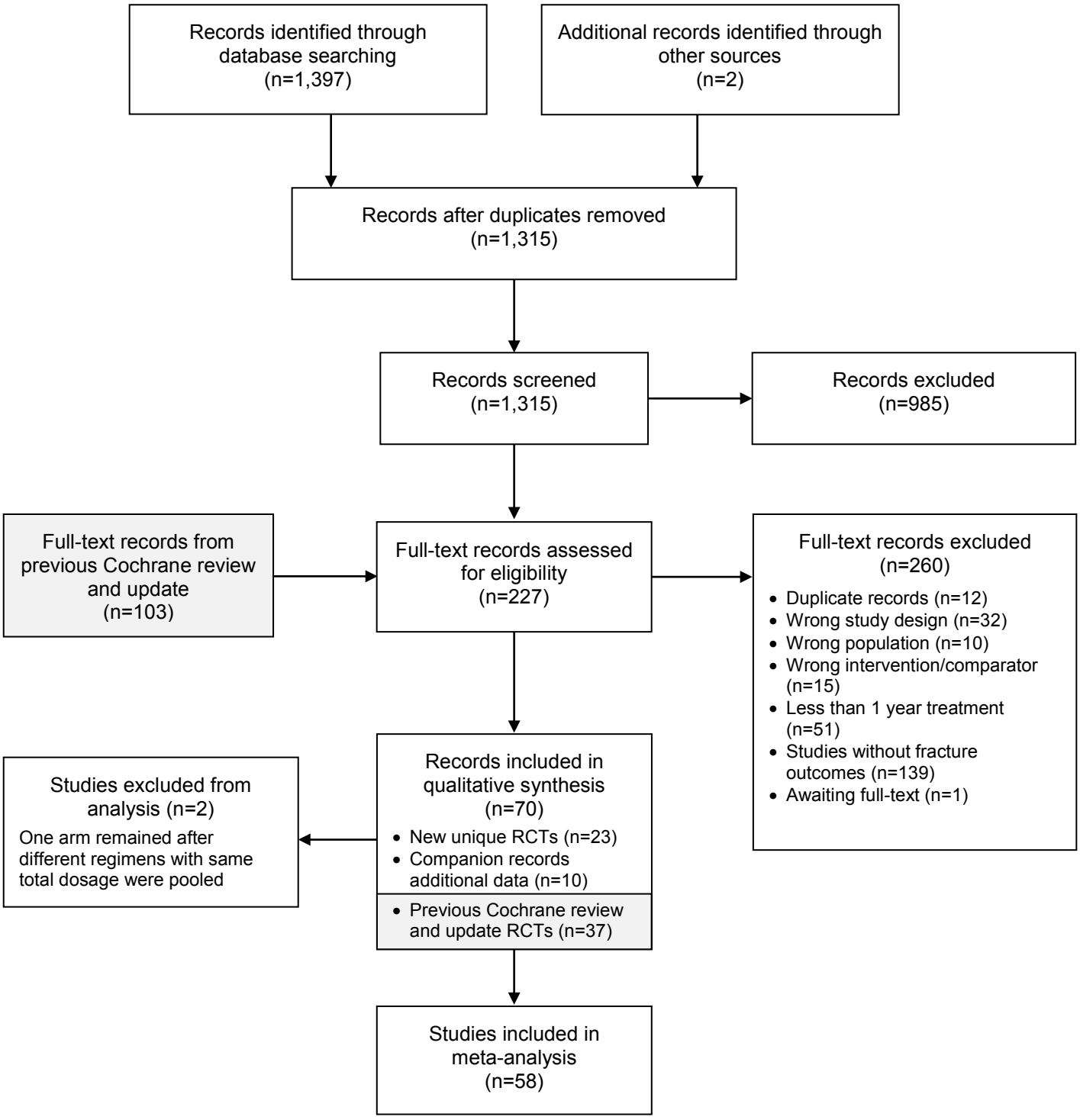


Table 3.3: Included studies in systematic review

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Akyol 2006	-	1 year	Secondary	Postmenopausal ≥ 1 yr, OP diagnosis based on WHO criteria (T-score <-2.5).	56.7 (8.0)	-2.9 (0.6)	-	ALE 70 mg/wk RIS 35 mg/wk	Oral	CAL 1000 mg	112
Ascott-Evans 2003	-	1 year	Primary	Age < 80 yrs, postmenopausal ≥ 3 yrs, used HRT for ≥ 1 yr and discontinued within 3 mo of joining study, T-score between -1.5 and -3.5.	57.3 (6.6)	-2.3 (0.7)	0%	Placebo ALE 10 mg/d	Oral	CAL 500 mg	144
Black 1996	FIT I (Vertebral Fractures)	3 years	Secondary	Age 55 to 81 yrs, postmenopausal ≥ 2 yrs, BMD more than 2 SD below PBM, at least 1 vertebral deformity.	70.8 (5.6)	-	100%	Placebo ALE 5-10 mg/d*	Oral	*CAL intake <1000 mg:* VID 250 IU CAL 500 mg	2027
Black 2006	FLEX (FIT extension)	5 years	Secondary	In FIT, assigned to receive ALE, completed ≥ 3 yrs of treatment. Ineligible if TH T-score <-3.5 or lower than FIT baseline.	73.2 (5.7)	-1.3	34%	Placebo ALE 5 mg/d ALE 10 mg/d	Oral	VID 250 IU CAL 500 mg	1099
Body 2002	-	2 years (discontinued at 14 months)	Secondary	Aged 30-85 yrs, postmenopausal ≥ 5 yrs, ambulatory, free of other severe or chronically disabling conditions, LS/FN BMD <-2.5 SD below PBM.	65.5 (8.5)	-	-	ALE 10 mg/d TER 40 µg/d	Oral SC	VID 400-1200 IU CAL 100 mg	146
Bone 1997	Alendronate Elderly Osteoporosis Study	2 years	Secondary	Age 60 to 85 yrs, in good health apart from OP, LS BMD at least 2 SD below PBM.	70.7 (5.9)	-	37%	Placebo ALE 1 mg/d ALE 2.5 mg/d ALE 5 mg/d	Oral	CAL 500 mg	359
Bone 2000	-	2 years	Secondary	Age 42 to 82 yrs, postmenopausal, prior hysterectomy, LS BMD below 0.862 g/cm^2.	61.3 (8.0)	-2.5	-	Placebo ALE 10 mg/d CEE 0.625 mg/d Combination	Oral	VID ≤400 IU CAL 500 mg	425
Brown 2009	-	1 year	Secondary	Ambulatory, postmenopausal, in general good health, LS/TH T-score <−2, with ≥1 hip and ≥2 vertebrae evaluable by DXA.	64.4 (8.5)	-2.6 (0.8)	-	ALE 70 mg/wk DEN 60 mg/6m	Oral SC	VID 400-800 IU CAL 500 mg	1189
Chavez-Valencia 2014	-	1 year	Primary	Age 45 to 79 yrs, nonsurgical menopause, low BMD in the lumbar spine and/or right hip according to current diagnostic criteria.	58.3 (7.5)	-2.2 (0.8)	0%	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	VID 200 IU CAL 600 mg	104

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Chesnut 1995	-	2 years	Secondary	Age 42 to 75 yrs, postmenopausal > 5 yrs, LS-BMD approximately 2 SD below PBM.	63.0 (6.3)	-	0%	Placebo ALE 5 mg/d ALE 10 mg/d ALE 20 mg/d* ALE 40 mg/d* ALE 2.5-40 mg/d*	Oral	CAL 500 mg	188
Cummings 1998	FIT II (Clinical Fractures)	4 years	Primary	Age 55 to 80 yrs, postmenopausal ≥ 2 yrs, FN BMD <0.68g/cm^2 (around 2 SDs below PBM), no vertebral fracture.	67.7 (6.2)	-	0%	Placebo ALE 5-10 mg/d*	Oral	*If CAL<1000 mg, instructed to take:* VID 250 IU CAL 500 mg	4432
Dursun 2001	-	1 year	Secondary	LS or FN-BMD at least 2 SDs or more below YAM.	61.2 (7.9)	-	-	Placebo CT 100 IU/d ALE 10 mg/d	Oral IN Oral	CAL 1000 mg	151
Eviö 2004	-	1 year	Secondary	Age 65 to 80 yrs, postmenopausal, with FN or LS BMD at least 2.5 SD below the PBM.	70.8	-	-	ALE 10 mg/d E2 2mg/d + NETA 1 mg/d Combination	Oral	*Based on dietary CAL intake, instructed to take:* VID 400 IU CAL 500-1000 mg	90
Freemantle 2012	-	2 years	Secondary	Age > 55 yrs, postmenopausal, ambulatory, LS/TH/FN BMD T-scores -2 to -4.	65.2 (7.6)	-	-	ALE 70 mg/wk DEN 60 mg/6m	Oral SC	VID ≥ 400 IU CAL 1000 mg	250
Galesanu 2011	-	3 years	Secondary	Postmenopausal, OP diagnosis based on WHO criteria (BMD more than 2.5 SD below PBM).	63.3 (3.1)	-	-	ALE 79 mg/wk RIS 35 mg/wk IBA 150 mg/m	Oral	Not reported	198
Galesanu 2015	-	3 years	Secondary	Postmenopausal women	66.0	-	-	ALE 70 mg/wk DEN 60 mg/6m	Oral SC	ALF 1 µg CAL 1000 mg	105
Greenspan 1998	-	30 months	Secondary	Age > 65 yrs, entry criteria were not based on BMD.	71.1 (4.6)	-	-	Placebo ALE 5-10 mg/d*	Oral	*CAL intake <1000 mg:* VID 125 IU CAL 250 mg	122
Greenspan 2002	-	2 years	Secondary	Age > 65 yrs, lives in local long-term care facilities, but not facilities that house independent, community-dwelling elderly persons, with LS or TH T-score <-2.0.	78.5	-	-	Placebo ALE 10 mg/d	Oral	VID 400 IU CAL 500 mg	327
Hadji 2012	ROSE	1 year	Secondary	Age 55–90 yrs, postmenopausal, with TH or LS T-score ≤ −2.0 and clinical risk factors.	53.9 (8.0)	-2.7 (1.2)	-	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	VID 800 IU CAL 1200 mg	599
Hagino 2009	-	1 year	Secondary	Age ≥ 45 yrs, postmenopausal, with BMD below 70% YAM or (T-score < −2.6), or BMD below 80% YAM (T-score < −1.7) with one fragility fracture.	64.9 (6.8)	-3.1 (0.5)	33%	ALE 5 mg/d MIN 1 mg/d	Oral	CAL 200 mg	269

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Hosking 1998	-	2 years	Primary	Postmenopausal ≥ 6 months, in good health, with no clinical or laboratory evidence of systemic disease.	53.3 (4.0)	-	-	Placebo ALE 2.5 mg/d ALE 5 mg/d HRT*	Oral	No supplementation	1460
IRIS 2012	-	1 year	Secondary	Age > 50 yrs, postmenopausal ≥ 3 yrs, ambulatory, LS/FN T-score <-2.5 SD or LS/FN T-score <-1 with ≥ 1 prevalent low-trauma fracture.	63.6 (7.2)	-2.9 (0.8)	-	ALE 70 mg/wk STR 2 g/d	Oral	VID 800 IU CAL 1000 mg	387
IRIS 2010	-	2 years	Secondary	Age ≥ 50 yrs, postmenopausal ≥ 5 yrs, ambulatory, Caucasian, LS/FN/TH T-score ≤ -2.5.	63.8 (7.3)	-2.8 (0.8)	16%	ALE 70 mg/wk STR 2 g/d	Oral	VID 400 IU CAL 500 mg	88
Iwamoto 2005	-	1 year	Secondary	Age 55 to 86 yrs, postmenopausal, having OP defined as BMD < 70% of YAM or 70-80% of YAM with osteoporotic fractures.	70.7 (7.3)	-	-	ALE 5 mg/d ETI 200 mg/d	Oral	CAL 800 mg	50
Iwamoto 2008	-	1 year	Secondary	Postmenopausal women diagnosed with OP as BMD < 70% of YAM or 70-80% of YAM with history of osteoporotic fractures.	69.4 (7.4)	-	54%	ALE 5 mg/d RAL 60 mg/d	Oral	CAL 800 mg	122
Jokar 2016	-	1 year	Secondary	Postmenopausal, OP with T-score ≤ -2.5.	-	-	-	ALE 70 mg/wk ALE 70 mg/wk +MK 10 mg/d	Oral	VID 400 IU CAL 1000 mg	47
Kaya 2009	-	1 year	Secondary	Diagnosed with osteoporosis with LS/FN T-score <-2.5.	61.7 (7.2)	-	-	ALE 70 mg/wk STR 2 g/d	Oral	VID 800 IU CAL 1200 mg	41
Kendler 2010	STAND	1 year	Secondary	Age > 55 yrs, postmenopausal, ambulatory, LS/TH BMD T-score ≤ 2 and > 4, received alendronate treatment equivalent to 70 mg/week for ≥ 6 months.	67.6 (7.8)	-2.6 (0.8)	-	ALE 70 mg/wk DEN 60 mg/6m	Oral SC	VID 400 IU CAL 100 mg	504
Kushida 2002	-	3 years (1 year extension)	Secondary	Women and men with OP, age > 65 yrs, capable of walking, with 1-4 vertebral fractures.	72.7 (5.8)	-	100%	ALE 5 mg/d ALF 1 µg/d	Oral	CAL 200 mg	365
Lewiecki 2007	-	2 years	Secondary	Age < 80 yrs, LS-BMD T-score -1.8 to -4.0 or FN/TH T-score of -1.8 to -3.5 at the femoral neck or total hip.	62.5 (8.2)	-2.1 (0.8)	-	Placebo ALE 70 mg/wk DEN (7 arms)*	SC Oral SC	VID 400 IU CAL 1000 mg	412
Li 2010	-	1 year	Secondary	Age 49-75 yrs, postmenopausal ≥ 1 yr, ambulatory, BMI 18–35 kg/m², LS/FN T-score ≤ -2.	65.1 (7.3)	-	11%	ALE 70 mg/wk IBA 2 mg/3m	Oral IV	VID 200 IU CAL 500 mg	158
Liberman 1995	Alendronate Phase III Osteoporosis Treatment Study	3 years	Secondary	Age 45 to 80 yrs, postmenopausal ≥ 5 yrs, with LS BMD at least 2.5 SD below PBM.	64.0	-	21%	Placebo ALE 5 mg/d ALE 10 mg/d ALE 20-5 mg/d*	Oral	CAL 500 mg	881

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Lindsay 1999	-	1 year	Secondary	Age > 40 yrs, or > 25 yrs if surgically menopausal, postmenopausal ≥ 5 yrs, receiving HRT ≥ 1 yr before study for OP, LS/FN BMD at least 2 SD below PBM; BMD at other sites 1.5 SD below PBM.	61.7 (8.0)	-2.4 (0.1)	-	ALE 10 mg/d+ HRT HRT	Oral	VID 400 IU CAL 1000 mg	428
Luckey 2004	EFFECT	1 years	Secondary	Age > 40 yrs, or > 25 yrs if surgically menopausal, postmenopausal >18 months, with OP (LS/TH BMD at least 2 SD below PBM), in good general health, spinal anatomy suitable for DXA.	64.2 (9.9)	-2.5 (0.7)	-	ALE 70 mg/wk RAL 60 mg/d	Oral	VID 200 IU CAL 500 mg	456
Luckey 2003[1]	-	1 year	Primary	Age 40 to 70 yrs, postmenopausal 6-12 months, LS and FN BMD T-score between 2.5 and 1.0, no history of spine or hip osteoporotic fracture, no prevalent vertebral fracture.	56.2 (5.9)	-	0%	ALE 5 mg/d ALE 35 mg/wk	Oral	VID 250 IU CAL 500 mg	723
McClung 1998	-	3 years	Primary	Age 40 to 59 yrs, healthy, postmenopausal 6 to 36 months.	41.5 (0.4)	-	0%	Placebo ALE 1 mg/d ALE 5 mg/d ALE 10 mg/d ALE 20 mg/d*	Oral	CAL 500 mg	447
Michalska 2006	-	2 years	Secondary	Age 50 to 80 yrs, postmenopausal, with LS BMD T-score <-2.5, and previous treatment with alendronate (10 mg/d) ≥ 3 yrs, but did not participate in any clinical trials.	65.2 (6.7)	-	-	Placebo ALE 10 mg/d RAL 60 mg/d	Oral	VID 800 IU CAL 500 mg	99
Miller 2008	MOTION	1 year	Secondary	Age 55 to 84 yrs, postmenopausal ≥ 5 yrs, ambulatory, mean LS BMD T-score <–2.5 and ≥ –5.	65.6	-3.2	-	ALE 70 mg/wk IBA 150 mg/m	Oral	VID 400 IU CAL 500 mg	1733
Murphy 2001	-	18 months	Secondary	Postmenopausal ≥ 4 yrs, good health, FN BMD at least 2 SD below the PBM, less than 3 SD below age-specific mean.	72.1 (4.9)	-	-	Placebo ALE 10 mg/d MK-677 25 mg/d Combination	Oral	CAL 500 mg	292
Muschitz 2014	CONFORS	1.5 years	Secondary	Postmenopausal, TER therapy for 9 mo, demonstrated “unsatisfactory clinical response to previous antiresorptive therapy” (*i.e.,* new vertebral fracture in 2 yrs of treatment and/or bone loss 3.5%/yr, discontinuation due to side-effects), T-score <–2.5 or have at least 2 FRAX clinical risk factors.	72.0 (7.6)	-	69%	TER 20 µg/d TER+ALE 70 mg/wk TER+RAL 60 mg/d	SC SC+Oral SC+Oral	Not reported	117

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Nabhan 2008	-	1 year	Secondary	Presence of osteoporosis (BMD less than -2.5 SD below mean reference value for a young adult, T-score < -2.5).	53.9 (6.6)	-3.2 (0.7)	0%	ALE 70 mg/wk ISO 20 mg/d	Oral	VID 400 IU CAL 500 mg	60
Nakamura 2014	DIRECT	2 years	Secondary	Postmenopausal women and men, age > 50 yrs, with 1-4 vertebral fractures, LS or TH BMD < 80% Japanese YAM.	69.6 (7.5)	-2.7 (1.8)	98%	Placebo ALE 35 mg/wk DEN 60 mg/6m	SC Oral SC	VID 400 IU CAL 600 mg	1194
Orimo 2011	-	2 years	Secondary	Age >70 yrs, postmenopausal, with ≥ 1 risk factor for new fractures (e.g., prevalent vertebral fractures, BMD < 3 SD of PBM, higher bone turn over marker levels).	76.6 (4.9)	-	56%	ALE 5 mg/d ALE 5 mg/d +ALF 1 µg/d	Oral	Not reported	2164
Palomba 2002	-	2 years	Secondary	Hysterectomy with bilateral oophorectomy performed before natural menopause, LS BMD at least 2.5 SD below the mean bone density of the peak value for sex-matched healthy young adults (T-score < -2.5).	61.1 (3.8)	-	-	ALE 10 mg/d E2 2 mg/d Combination	Oral	VID 20 IU CAL tablet to achieve total daily dose >1000 mg	150
Palomba 2005	-	1 year	Secondary	Natural menopause, LS BMD at least 2.5 SD below the PBM of healthy young women (T-score < -2.5).	64.9 (4.1)	-3.2 (0.5)	-	ALE 10 mg/d CEE 0.625 mg/d +MP 2.5 mg/d RAL 60 mg/d ALE+RAL ALE+HRT	Oral	*CAL intake <1000 mg:* CAL 500 mg	1100
Panico 2011	-	1.5 years	Secondary	Postmenopausal OP (LS/FN T-score ≤ -2.5), presence of 2 osteoporotic vertebral fractures, previous treatment for osteoporosis.	62.6 (12.1)	-3.9 (0.7)	99%	ALE 70 mg/d TER 20 µg/d	Oral SC	VID 800 IU CAL 1000 mg	81
Recker 2007	EVA	5 years (early termination at 1 year)	Secondary	Age 50 to 80 yrs inclusive, postmenopausal ≥ 2 yrs, ambulatory, FN BMD between 2.5 and 4 SD inclusive below average bone mass for young women, no prevalent vertebral fractures.	65.6 (7.8)	-2.3 (1.0)	0%	ALE 10 mg/d RAL 60 mg/d	Oral	VID 400 IU CAL 500 mg	1423
Pols 1999	FOSIT	1 year	Secondary	Age < 85 yrs, postmenopausal ≥ 3 yrs, LS BMD at least 2 SDs below mean of premenopausal women, in good health.	62.8 (7.4)	-	-	Placebo ALE 10 mg/d	Oral	CAL 500 mg	1908
Robles-Carranza 2013	-	3 years	Primary	Postmenopausal women with low BMD and no other explanation for bone disease or previous fractures.	61.0 (9.6)	-	-	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	VID 400 IU CAL 1200 mg	118

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Russo 1996	-	1 year	Secondary	Age 50 to 77 yrs, postmenopausal ≥ 1 yr, BMD lower than mean value in normal population -2.5 SD (Z-score) in 2 sites.	64.1 (6.2)	-	0%	ALE 5 mg/d ETI 400 mg/d (C) CLO 100 mg/wk-400 mg/d (C)	Oral Oral IM, Oral	Not reported	77
Sambrook 2004	EFFECT-International	1 year	Secondary	Postmenopausal ≥ 6 months, LS/TH BMD at least 2 SD below young normal mean); in good general health.	61.6 (8.0)	-2.8 (0.8)	26%	ALE 70 mg/wk RAL 60 mg/d	Oral	Given in accordance with local standard care	487
Sarioglu 2006	-	1 year	Secondary	Postmenopausal women with osteoporosis.	58.8 (6.9)	-	10%	ALE 70 mg/wk RIS 5 mg/d	Oral	VID 400 IU CAL 1000 mg	50
Sawada 2009	-	1 year	Primary	Age 36 to 65 yrs, Japanese, natural or surgically postmenopausal (≥ 6 months and <15 yrs), with OP (BMD below 2.5 SD of PBM) or osteopenia (-2.5 to -1.5 SD).	59.3 (5.3)	-	0%	ALE 5 mg/d ALF 1 µg/d	Oral	CAL 600 mg	32
Schnitzer 2000[1]	-	1 year	Secondary	Age 40 to 90 yrs, postmenopausal ≥2 yrs, with LS and/or FN BMD T-score ≤-2.5 or history of osteoporotic fracture.	66.5	-	17%	ALE 10 mg/d ALE 35 mg x2/wk ALE 70 mg/wk	Oral	VID 250 IU CAL 500 mg	1258
Tan 2016	-	3 years	Secondary	Diagnosed with postmenopausal osteoporosis at Huashan Hospital and Huadong Hospital based on WHO criteria (FN, LS, TH T-score ≤ -2.5).	68.0 (8.8)	-	-	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	Not reported	105
Tseng 2006	-	3 years	Secondary	BMD below -2 SD of the young adult at either lumbar spine (L2-L4) or hip.	61.0 (1.0)	-	0%	ALE 10 mg/d+HRT HRT	Oral	CAL 500 mg	151
Yan 2009	-	1 year	Secondary	Age ≤ 85 yrs, ambulatory postmenopausal ≥3 yrs, no prevalent vertebral fractures, LS BMD at least 2 SD below the mean bone mass of normal young Chinese women.	64.9 (6.2)	-	0%	Placebo ALE 70 mg/wk	Oral	*If levels are low:* VID 200 IU CAL 500 mg	560
Zhang 2015	-	1 year	Secondary	Age > 55 yrs, postmenopausal ≥ 1 yr, either LS/TH/FN BMD T-score ≤ -2.5 or LS/TH/FN BMD T-score ≤ -1.5 and prior fragility fracture (spine, wrist, humerus, or clavicle).	65.2 (7.7)	-	-	ALE 70 mg/wk+ VID 5600 IU CLC 0.25 µg/d	Oral	CAL 500 mg	219
Shiraki 1999	-	48 weeks	Secondary	Primary OP (LS BMD ≥ 2.5 SD below YAM, or ≥ 1.5 SD with ≥ 1 vertebral fractures), no prior bisphosphonate treatment.	63.3 (0.7)	-	16%	ALE 5 mg/d ALF 1 µg/d	Oral	CAL 200 mg	210

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Qin 2007	-	1 year	Secondary	Age 50 to 75 yrs, postmenopausal, with fracture at distal radius in the past 5 yrs, and LS or hip T-score <-2.	59.8 (6.3)	-2.2 (0.8)	-	Placebo ALE 10 mg/d	Oral	CAL 1200 mg	47

Abbreviations: OP=osteoporosis, WHO=World Health Organization, IRIS=Institut de Recherches Internationales Servier, BMD=bone mineral density, PBM=peak bone mass, YAM=young adult mean, SD=standard deviation, LS=lumbar spine, FN=femoral neck, TH=total hip. IM=intramuscular, IV=intravenous, IN=intranasal, SC=subcutaneous, C=cyclic regimen, m=months, yr=year, d=day, wk=week. ALE=alendronate, ETI=etidronate, RIS=risedronate, IBA=ibandronate, ZOL=zoledronic acid, CLO=clodronate, MIN=minodronate, PAM=pamidronate, DEN=denosumab, RAL=raloxifene, CT=calcitonin, HRT=hormone replacement therapy, CLC=calcitriol, CEE=conjugated equine estrogen, E2=estradiol, NETA=norethisterone acetate (progestin), MP=medroxyprogesterone (progestin), ISO=isosorbide mononitrate, ALF=alfacalcidol, MK=menatetrenone (vitamin K), MK-677=ibutamoren, PHO=phosphate, NG=norgestrel, VID=vitamin D, CAL=calcium, IU=international units.

[1]The studies Lucky 2003 and Schnitzer 2000 were not included in the analysis due to having one arm after pooling regimens with the same total dose (*e.g.,* ALE 5 mg/d and ALE 35 mg/wk).

*Study regimens and dose changes of interest

Black 1996: Alendronate dose increased from 5 mg/d to 10 mg/d at the 24 month visit.
Chesnut 1995: Alendronate 20 and 40 mg/d doses changed to placebo at 12 months.
Cummings 1998: Alendronate dose increased from 5 mg/d to 10 mg/d at the 24 month visit.
Greenspan 1998: Alendronate dose was 5 mg/d until 18 months, and changed to 10 mg/d from 18-30 months.
Hosking 1998: For HRT, US centers administered CEE 0.625 mg/d+MP 5 mg/d while European centers gave a cyclic regimen of E2 2 mg/d+NETA 1 mg/d.
Lewiecki 2007: 7 denosumab arms: 6, 14, or 30 mg per 3m; 14 mg, 60, 100, or 210 mg per 6m.
Liberman 1995: Alendronate dose was 20 mg/d for 2 years followed by 5 mg/d for 1 year.
McClung 1998: Alendronate 20 mg/d for 2 years, placebo in third year.

3.3.2 RISK OF BIAS

Risk of bias assessments are presented in Table 3.4. Three studies had low risk of bias across all domains (61, 91, 92), no study had high risk of bias across all domains. Of 58 studies, 24 had low risk of bias for random sequence generation and 13 for allocation concealment. One study had high risk of bias in both random sequence generation and allocation concealment domains due to describing that participants were randomized “in the order of recruitment” (93). Half of the studies (29/58, 50%) had unclear risk of bias for random sequence generation and allocation concealment due to lack of information provided in the study reports. All objective outcomes had low risk of bias for blinding, while 21 studies had low risk of bias and the same number had high risk of bias for subjective outcomes. Four studies did not have any subjective outcomes extracted thus the domain of blinding for subjective outcomes is ‘not applicable’. More than half of studies (34/58, 59%) had low risk of bias for incomplete efficacy or safety outcome data (*i.e.,* had greater than 80% followup at end of trial, similar reasons and rates of attrition among treatment groups, analysis population was intent-to-treat or representative of randomized population), while 13 studies (22%) had high risk of bias for both. Most studies (46/58, 79%) had low risk of selective outcome reporting, and forty-three studies (74%) had low risk of other biases.

Figure 3.2: Risk of bias assessments summary

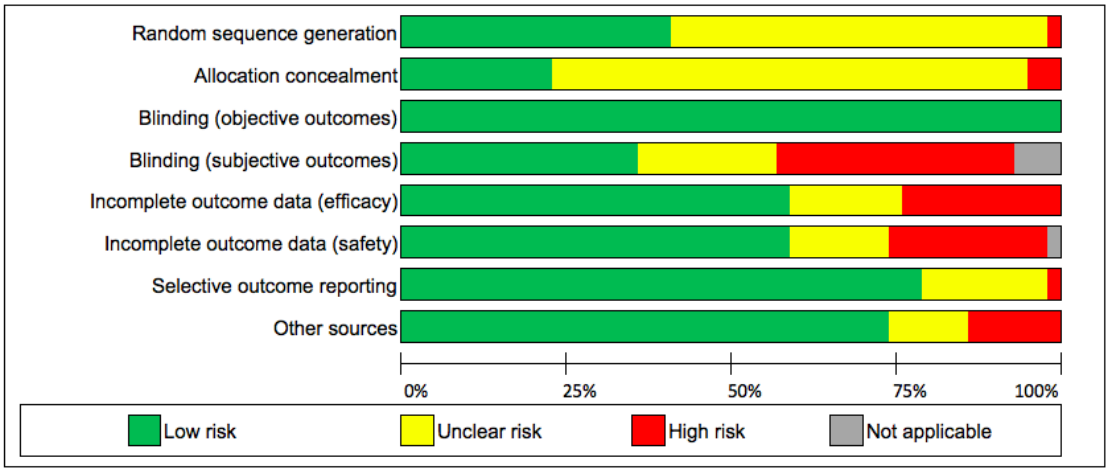


Table 3.4: Risk of bias assessments for 58 studies

Study	Random sequence generation	Allocation concealment	Blinding (objective outcomes)	Blinding (subjective outcomes)	Incomplete data (efficacy outcomes)	Incomplete data (safety outcomes)	Selective reporting	Other bias
Akyol 2006	Unclear	Unclear	Low	NA	High	High	Unclear	Unclear
Ascott-Evans 2003	Low	Low	Low	Low	Low	Low	Low	Low
Black 1996	Low	Low	Low	Low	Low	Low	Low	High
Black 2006	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low
Body 2002	Unclear	Unclear	Low	Low	High	High	Low	Unclear
Bone 1997	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Bone 2000	Low	Unclear	Low	Unclear	High	High	Low	Low
Brown 2009	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Chavez-Valencia 2014	Low	Unclear	Low	NA	Low	Low	Low	Low
Chesnut 1995	Unclear	Unclear	Low	High	Low	Low	Low	Low
Cummings 1998	Low	Low	Low	Low	Low	Low	Low	High
Dursun 2001	Unclear	Unclear	Low	High	Unclear	Unclear	Low	Low
Eviö 2004	Unclear	Unclear	Low	Low	High	High	Low	Low
Freemantle 2012	Low	Low	Low	High	Low	Low	Low	Low
Galesanu 2011	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	High
Galesanu 2015	Unclear	High	Low	High	Unclear	High	Unclear	Unclear
Greenspan 1998	Unclear	Unclear	Low	Unclear	High	High	Low	High
Greenspan 2002	Low	Unclear	Low	Low	Unclear	Unclear	Low	Low
Hadji 2012	Low	Unclear	Low	High	High	High	Unclear	Low
Hagino 2009	Low	Unclear	Low	Low	Low	Low	Low	Low
Hosking 1998	Unclear	Low	Low	High	Low	Low	Low	Low
IRIS 2010	Low	Low	Low	Low	Low	Low	High	Low
IRIS 2012	Unclear	Unclear	Low	Low	High	High	Low	Low
Iwamoto 2005	High	High	Low	High	Low	Low	Low	Low
Iwamoto 2008	Unclear	Unclear	Low	High	Low	Low	Low	Low
Jokar 2016	Unclear	Unclear	Low	High	Unclear	Unclear	Unclear	Unclear
Kaya 2009	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	High
Kendler 2010	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Kushida 2002	Unclear	Unclear	Low	Low	High	High	Low	High
Lewiecki 2007	Unclear	Unclear	Low	High	Low	Low	Unclear	Low

Study	Random sequence generation	Allocation concealment	Blinding (objective outcomes)	Blinding (subjective outcomes)	Incomplete data (efficacy outcomes)	Incomplete data (safety outcomes)	Selective reporting	Other bias
Li 2010	Unclear	Unclear	Low	High	Low	Low	Low	Low
Liberman 1995	Low	Unclear	Low	Low	Low	Low	Low	Low
Lindsay 1999	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Luckey 2004	Low	Low	Low	Low	Low	Low	Low	Low
McClung 1998	Low	Unclear	Low	Low	High	High	Low	Low
Michalska 2006	Unclear	Unclear	Low	High	Low	Low	Low	Low
Miller 2008	Low	Low	Low	Low	Low	Low	Low	Low
Murphy 2001	Unclear	Unclear	Low	NA	High	NA	Low	Unclear
Muschitz 2014	Unclear	High	Low	Unclear	Low	Low	Low	Low
Nabhan 2008	Low	Low	Low	High	Unclear	Unclear	Low	Low
Nakamura 2014	Unclear	Low	Low	High	Low	Low	Unclear	High
Orimo 2011	Low	Low	Low	High	High	High	Low	Unclear
Palomba 2002	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Palomba 2005	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Panico 2011	Unclear	Unclear	Low	High	Low	Low	Low	Low
Pols 1999	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Qin 2007	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Recker 2007	Low	Low	Low	Low	Low	Low	Low	High
Robles-Carranza 2013	Unclear	Unclear	Low	High	High	High	Unclear	Unclear
Russo 1996	Unclear	Unclear	Low	High	Unclear	Unclear	Low	Low
Sambrook 2004	Low	Low	Low	Low	Low	Low	Low	Low
Sarioglu 2006	Unclear	Unclear	Low	NA	Unclear	Unclear	Low	Low
Sawada 2009	Unclear	Unclear	Low	High	Low	Low	Low	Low
Shiraki 1999	Low	Unclear	Low	Low	High	High	Low	Low
Tan 2016	Low	Unclear	Low	High	Low	Low	Unclear	Low
Tseng 2006	Unclear	Unclear	Low	Unclear	High	High	Low	Low
Yan 2009	Low	Unclear	Low	Low	Low	Low	Low	Low
Zhang 2015	Unclear	Unclear	Low	High	Low	Low	Low	Low

*IRIS=Institut de Recherches Internationales Servier.

3.3.3 CHARACTERISTICS OF OUTCOMES

The total number of studies included for each outcome varied. The most commonly reported outcomes were non-vertebral fractures, hip fractures and withdrawal due to adverse events which each included 12 studies. Osteonecrosis of the jaw and fractures of the hip or wrist were the least commonly reported outcomes. Results are shown for the standard doses 10 mg/day or 70 mg/week and 5 mg/day or 35 mg/week compared to placebo for the main analysis, subgroup and sensitivity analyses. Additional comparisons are presented separately, including alendronate alone versus other active comparators, alendronate in combination with an intervention versus the same intervention, alendronate combined with an intervention versus placebo, and alendronate combined with a treatment versus a different treatment. Forest plots will be used to summarize the results.

3.3.4 RADIOGRAPHIC VERTEBRAL FRACTURES

3.3.4.1 MAIN ANALYSIS

Women who received alendronate 10 mg/day had a statistically significant 45% lower risk of sustaining a radiographic vertebral fracture compared to those who received placebo (95% CI: 0.45, 0.67), while the reduction was a statistically significant 44% for those receiving 5 mg/day compared to placebo (95% CI: 0.35, 0.90). Six studies provided data for the 10 mg dose (total 6907 participants), and four provided data for the 5 mg dose (total 1526 participants). Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.5: alendronate 10 mg/day versus active or combination treatment (comparisons 5.1.1 to 5.1.10), alendronate 5 mg/day versus active or combination treatment (5.1.11 to 5.1.16), alendronate combination with treatment versus the same treatment (5.1.17 to 5.1.18), alendronate combination with treatment versus placebo (5.1.19), and alendronate combination with treatment versus different treatment (5.1.20). Results for these comparisons were not pooled due to varying comparators.

Figure 3.3: Alendronate 10 mg versus placebo, radiographic vertebral fractures

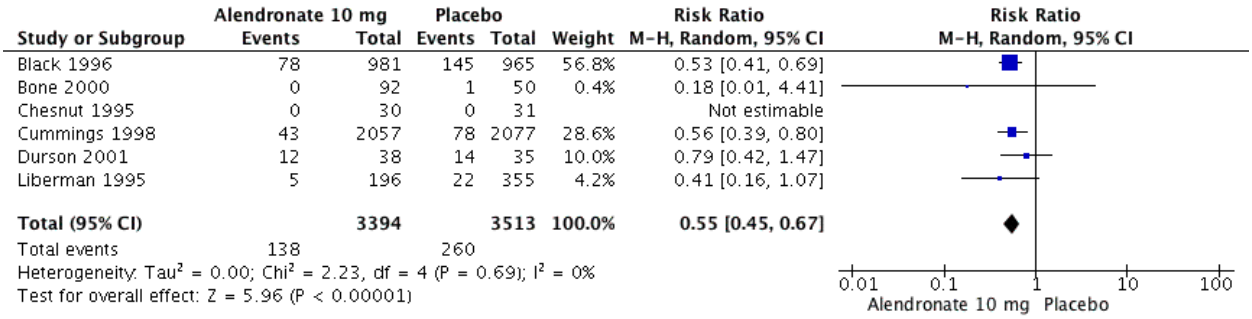


Figure 3.4: Alendronate 5 mg versus placebo, radiographic vertebral fractures

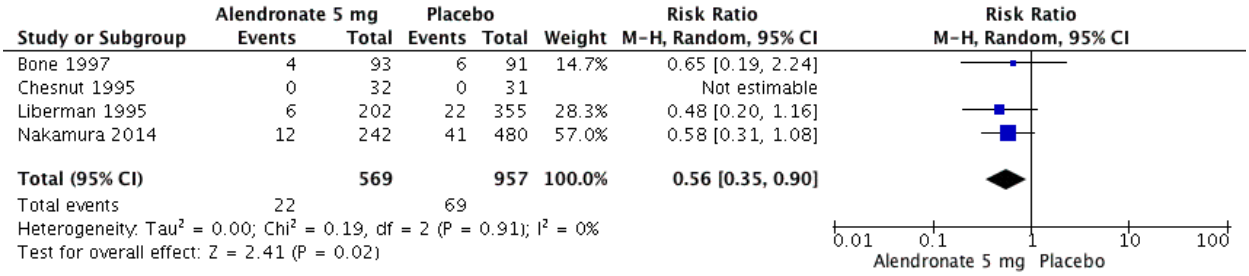
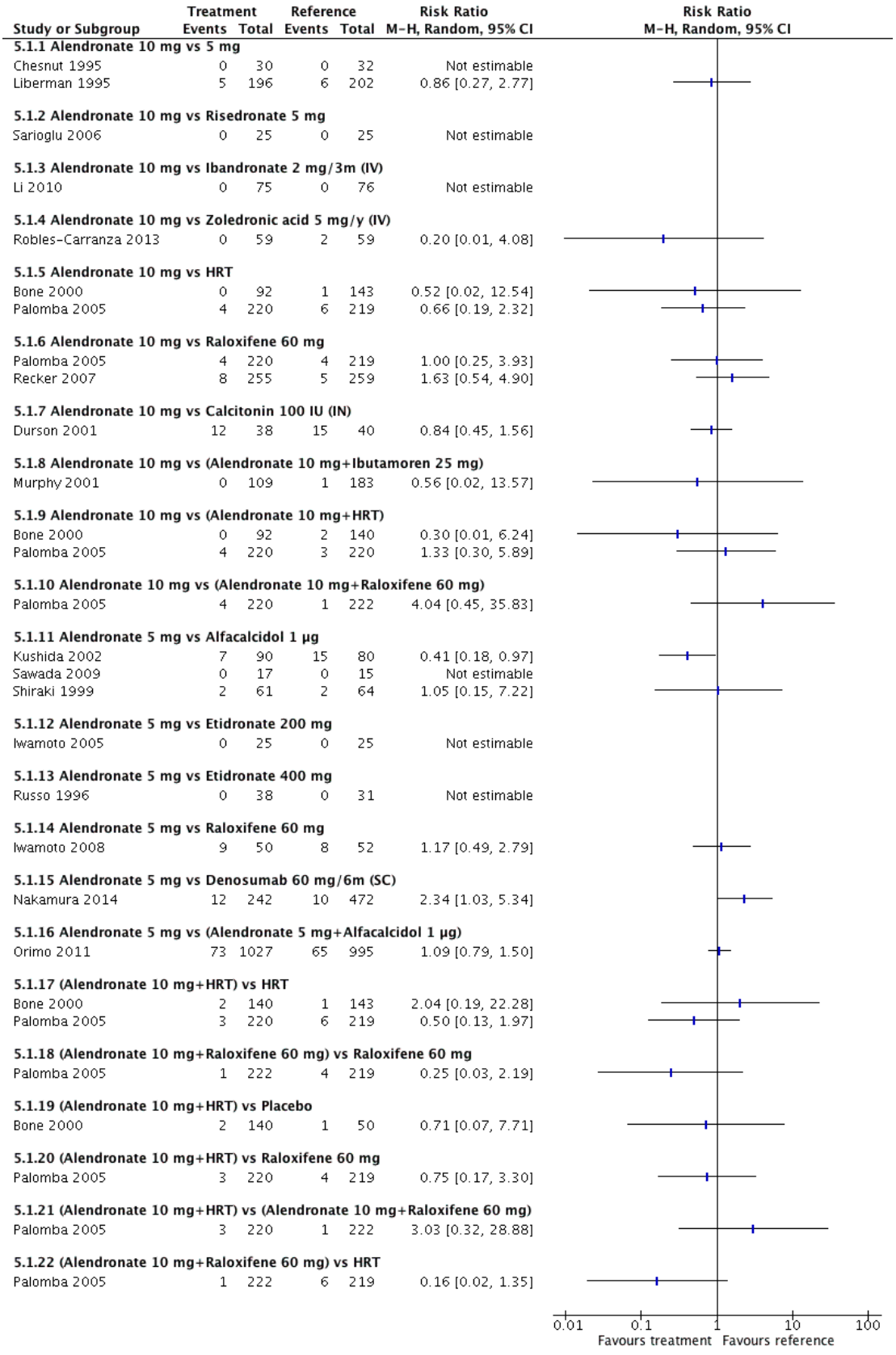


Figure 3.5: Alendronate versus active comparators or placebo, radiographic vertebral fractures



3.3.4.2 SUBGROUP ANALYSES

Five secondary prevention studies that compared alendronate 10 mg/day to placebo (Figure 3.6) showed similar risk reductions as the only primary prevention study (secondary RR 0.55, 95% CI: 0.43, 0.69; primary RR 0.56, 95% CI: 0.39, 0.80, subgroup differences p=0.95). FIT-II (85) was considered primary prevention due excluding participants with vertebral fractures. All studies that compared alendronate 5 mg/day to placebo were secondary prevention trials (Figure 3.7).

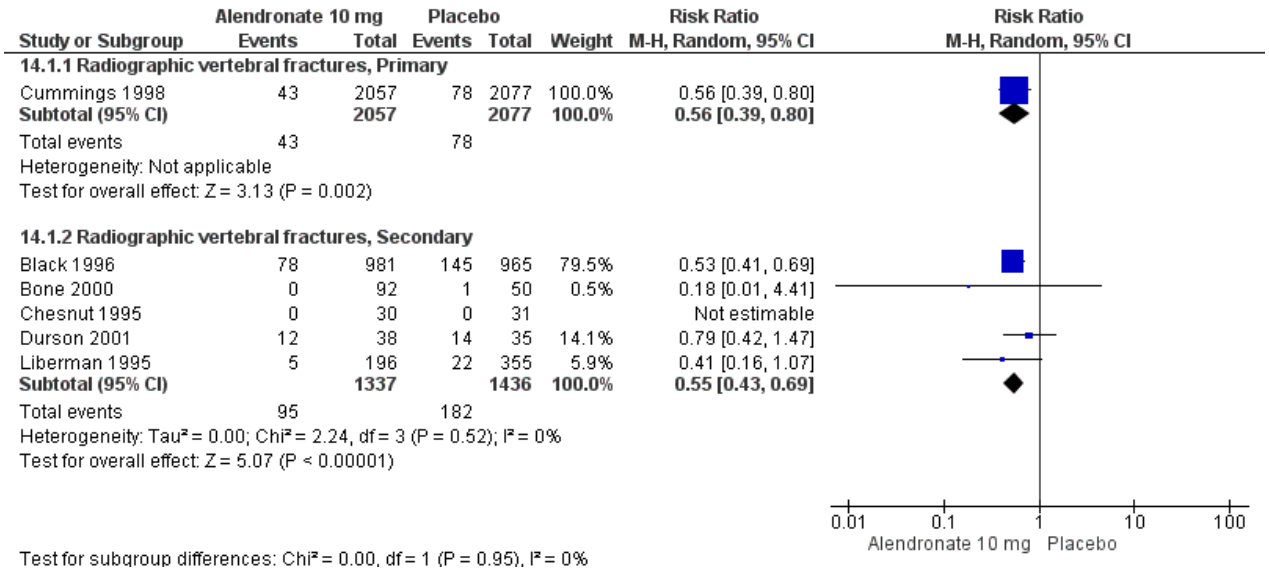
Trials containing bisphosphonate-naïve participants showed identical estimates to the main analysis (RR 0.55, 95% CI: 0.45, 0.67), however, it was significantly different from the FLEX trial (87) comprised of bisphosphonate-experienced participants (RR 0.86, 95% CI: 0.60, 1.24, subgroup differences p=0.04). The FLEX trial is an extension study that enrolled participants who completed at least 3 years of FIT. The randomized population had on average 5 years of prior alendronate treatment at baseline. Results of the individual study found alendronate was not significantly better than placebo for prevention of radiographic vertebral fractures.

Treatment durations ranged from one to five years among 10 mg/day dose comparisons, and one to three years among 5 mg/day doses. In the 10 mg dose, the test for subgroup differences was statistically significant (p=0.04). Studies providing data at two years of treatment had the lowest effect estimate indicating a significant 61% reduction in risk of fracture compared to placebo (95% CI: 0.28, 0.55) while the estimate at five years showed a null effect (RR 0.86, 95% CI: 0.60, 1.24). The FLEX trial was the only study that provided data at five years of treatment. A sensitivity analysis (Figure 3.6D) exploring potential reasons for subgroup differences and heterogeneity found that removal of five-year data resulted in loss of statistical significance among subgroups (p=0.20) and reduction of heterogeneity from substantial (I^2=60.6%) to low (I^2=34.7%). Generally, the effect estimates from FLEX appear closer to the null than other treatment durations. Unlike other trials, all participants from the study received previous long-term alendronate treatment, which may have made the placebo group more similar to the alendronate group compared to other years. The authors describe the study as a “discontinuation trial” with a discontinuation arm (placebo) and a

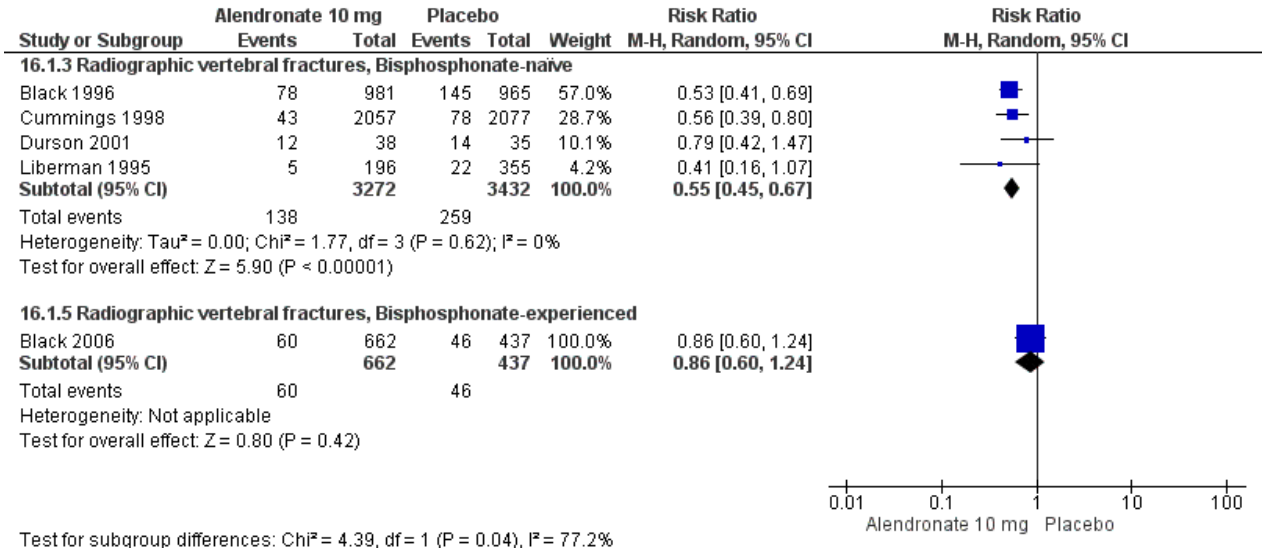
continuation arm (alendronate) as opposed to a placebo-controlled trial (87). Among 5 mg/day studies, risk ratios ranged from a 41% risk reduction at 2 years of treatment (95% CI: 0.34, 1.04) to a 52% risk reduction at three years of treatment compared to placebo (95% CI: 0.20, 1.16), but the differences were not statistically significant between subgroups.

Figure 3.6: Alendronate 10 mg versus placebo, radiographic vertebral fractures (subgroup)

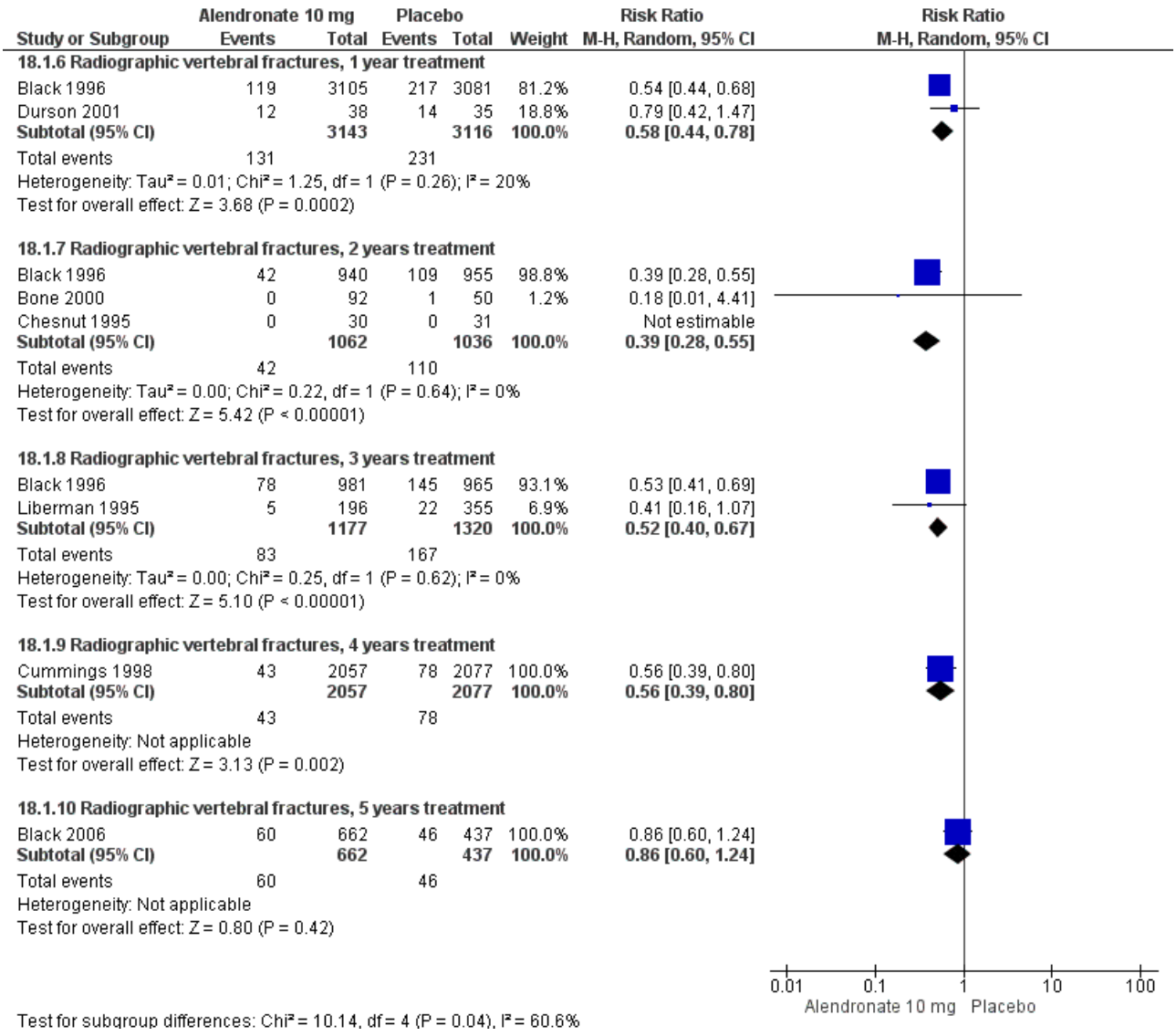
A) Primary or secondary prevention studies



B) Prior bisphosphonate experience



C) Treatment durations



D) Treatment durations (excluding data from the FLEX trial)

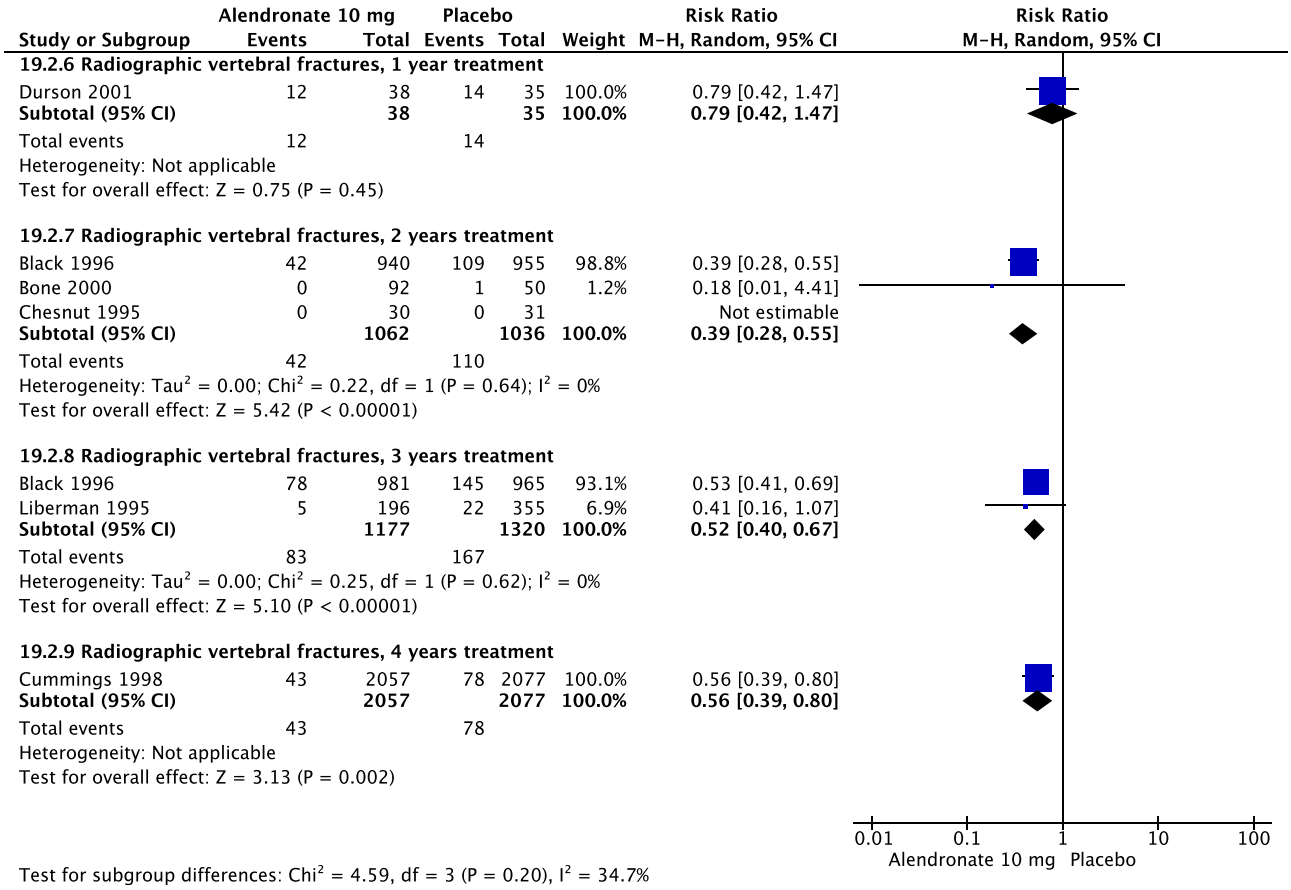
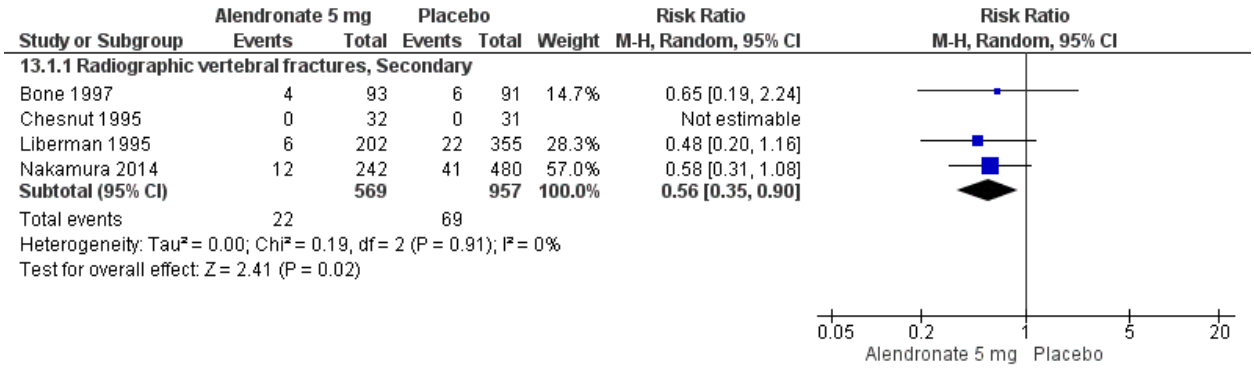
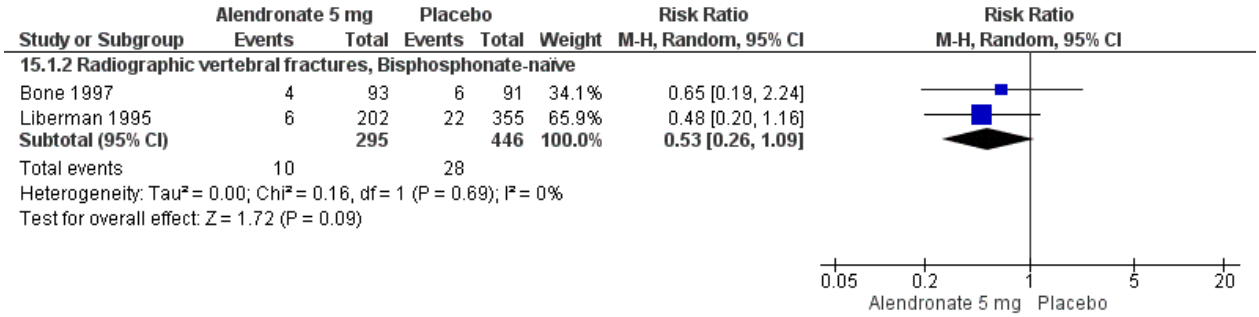


Figure 3.7: Alendronate 5 mg versus placebo, radiographic vertebral fractures (subgroup)

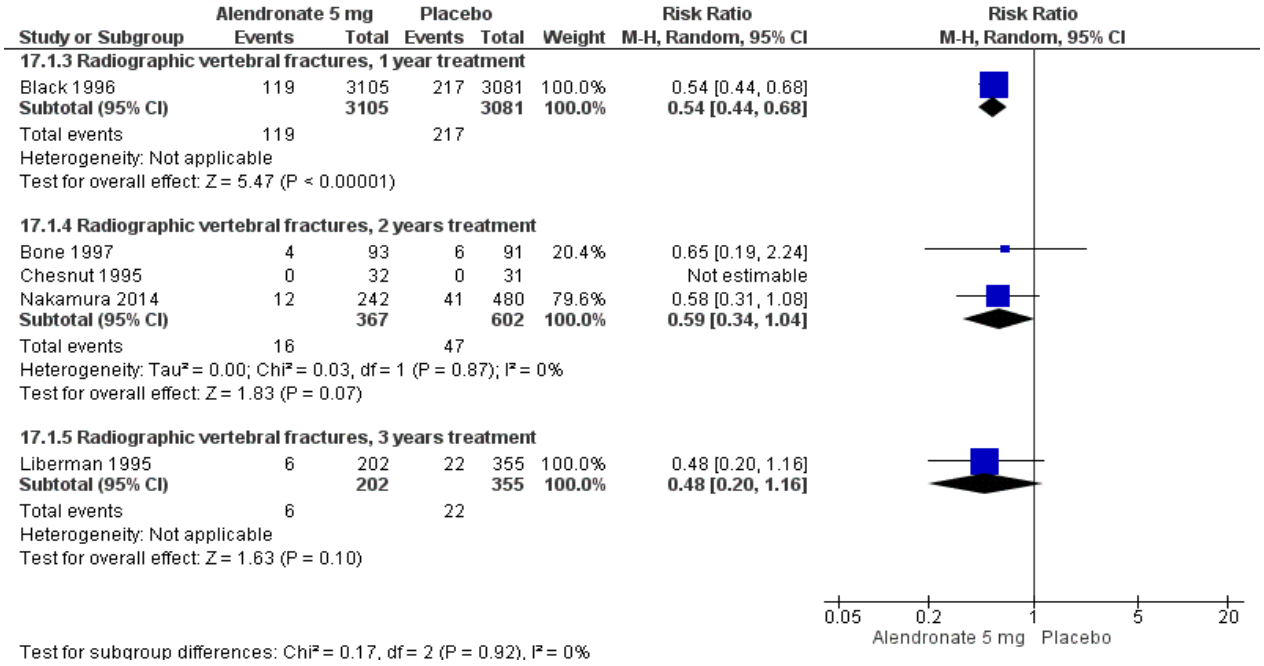
A) Primary or secondary prevention studies



B) Prior bisphosphonate experience



C) Treatment durations



3.3.4.3 SENSITIVITY ANALYSES

To test the robustness of the hierarchical classification for primary versus secondary prevention studies, all trials were re-classified using 2.5 SD instead of 2 SD for the BMD and T-score thresholds. Only one study changed prevention type under the new criteria (89), however it had zero events in all arms thus the analysis was not affected. The study was previously secondary for including participants with BMD 2 SD or more below the normal bone mass. Since the threshold changed to 2.5 SD, it was classified as primary prevention because it also excluded those with prevalent osteoporotic vertebral fractures.

Pooled risk ratios for low risk of bias studies did not differ significantly from the main analysis or between doses (10 mg RR 0.53, 95% CI: 0.43, 0.65; 5 mg RR 0.54, 95% CI: 0.33, 0.91). All except three studies had low risk of bias. Two studies had unclear risk of bias due to not reporting the withdrawal rate (80, 94), and one had high risk of bias due to having less than 80% followup and differing rates of attrition between groups (95).

No statistically significant differences were detected from the main analysis among studies with fractures as an efficacy outcome and when baseline denominators were used instead of those included in analysis for both doses.

Figure 3.8: Alendronate 10 mg versus placebo, radiographic vertebral fractures (sensitivity)

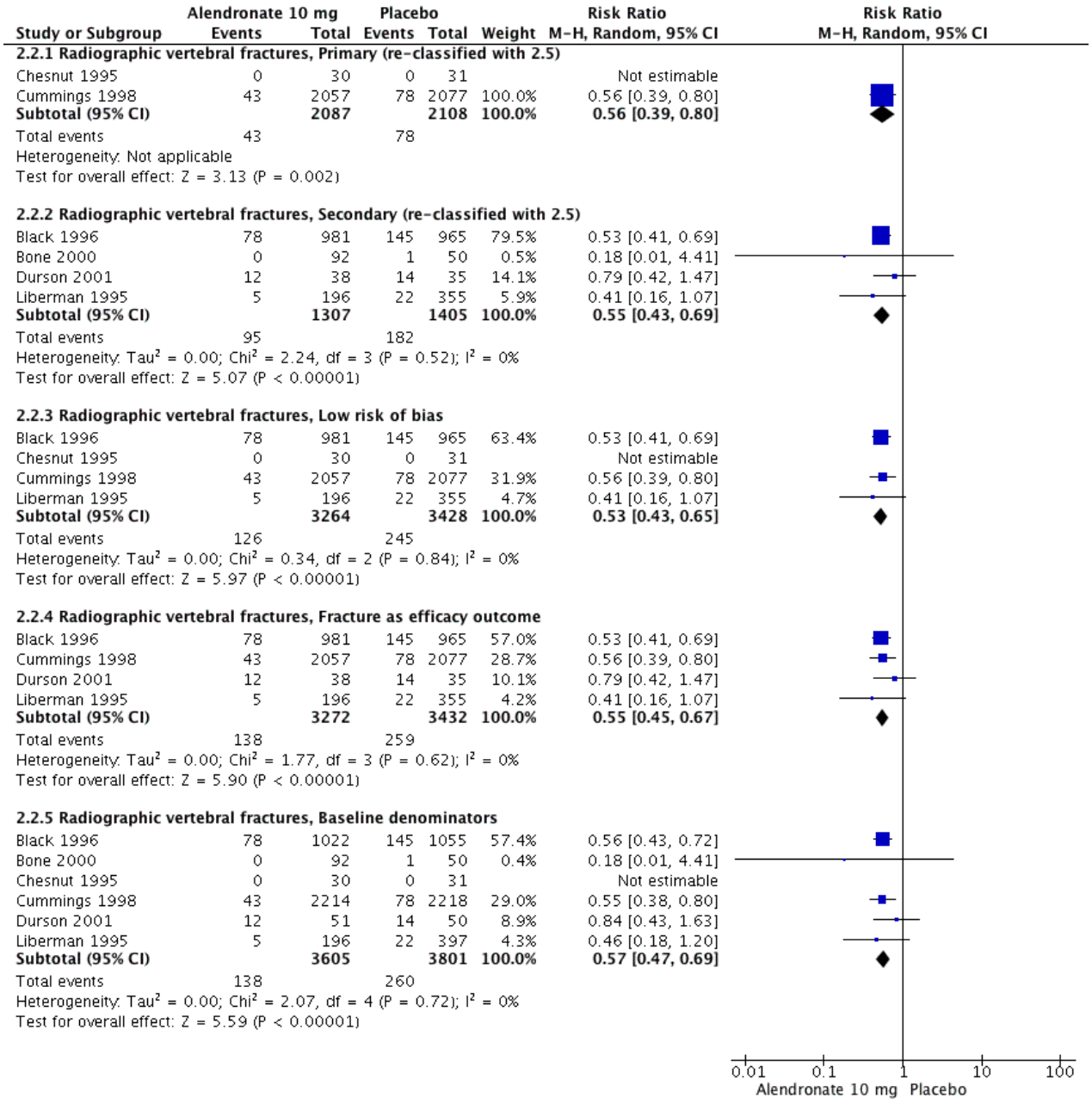
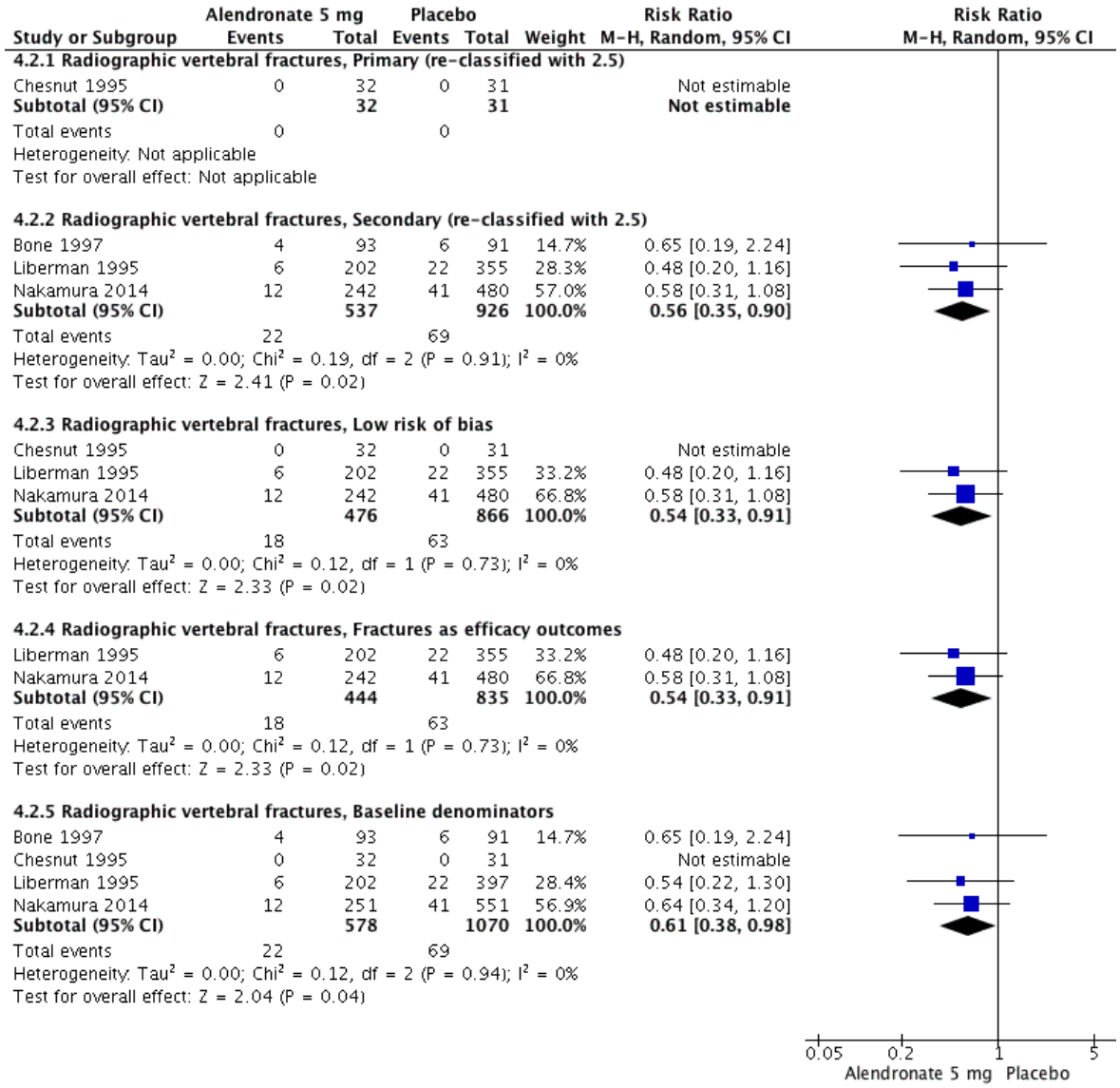


Figure 3.9: Alendronate 5 mg versus placebo, radiographic vertebral fractures (sensitivity)



3.3.5 CLINICAL VERTEBRAL FRACTURES

3.3.5.1 MAIN ANALYSIS

Women who received alendronate 10 mg/day had a statistically significant 55% lower risk of sustaining a clinical vertebral fracture compared to those who received placebo (95% CI: 0.28, 0.73). The only analyzable study for the 5 mg dose indicates it is no better than placebo. Seven studies provided data for the 10 mg dose (total 3109 participants), and two studies provided data for the 5 mg dose (total 1178 participants). Of these two studies, one reported zero fractures overall and did

not contribute to the analysis. Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.12, including alendronate versus single active comparators or combination treatments (comparisons 5.1.1 to 5.1.16), alendronate combination versus the same non-alendronate treatment (5.1.17 to 5.1.18) or placebo (5.1.19), and alendronate combination versus a different active treatment (5.1.20 to 5.11.22).

Figure 3.10: Alendronate 10 mg versus placebo, clinical vertebral fractures

	Alendronate 10 mg		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Ascott Evans 2003	0	95	0	49		Not estimable
Black 1996	23	981	50	965	94.8%	0.45 [0.28, 0.74]
Bone 2000	1	92	1	50	3.0%	0.54 [0.03, 8.50]
Lewiecki 2007	0	46	0	46		Not estimable
McClung 1998	0	88	1	90	2.2%	0.34 [0.01, 8.26]
Qin 2007	0	22	0	25		Not estimable
Yan 2009	0	280	0	280		Not estimable
Total (95% CI)		**1604**		**1505**	**100.0%**	**0.45 [0.28, 0.73]**
Total events	24		52			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.001)

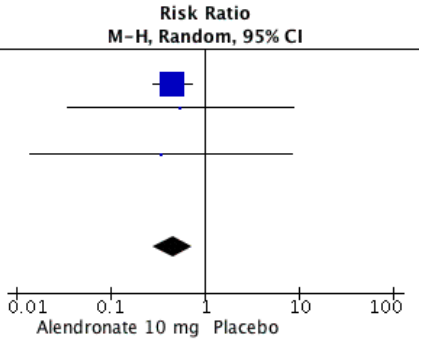


Figure 3.11: Alendronate 5 mg versus placebo, clinical vertebral fractures

	Alendronate 5 mg		Placebo		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI
Hosking 1998	0	498	0	502	Not estimable
McClung 1998	1	88	1	90	1.02 [0.06, 16.10]

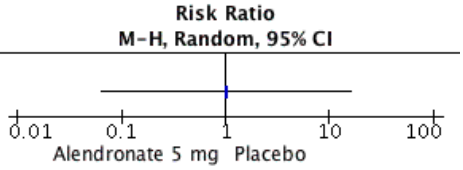
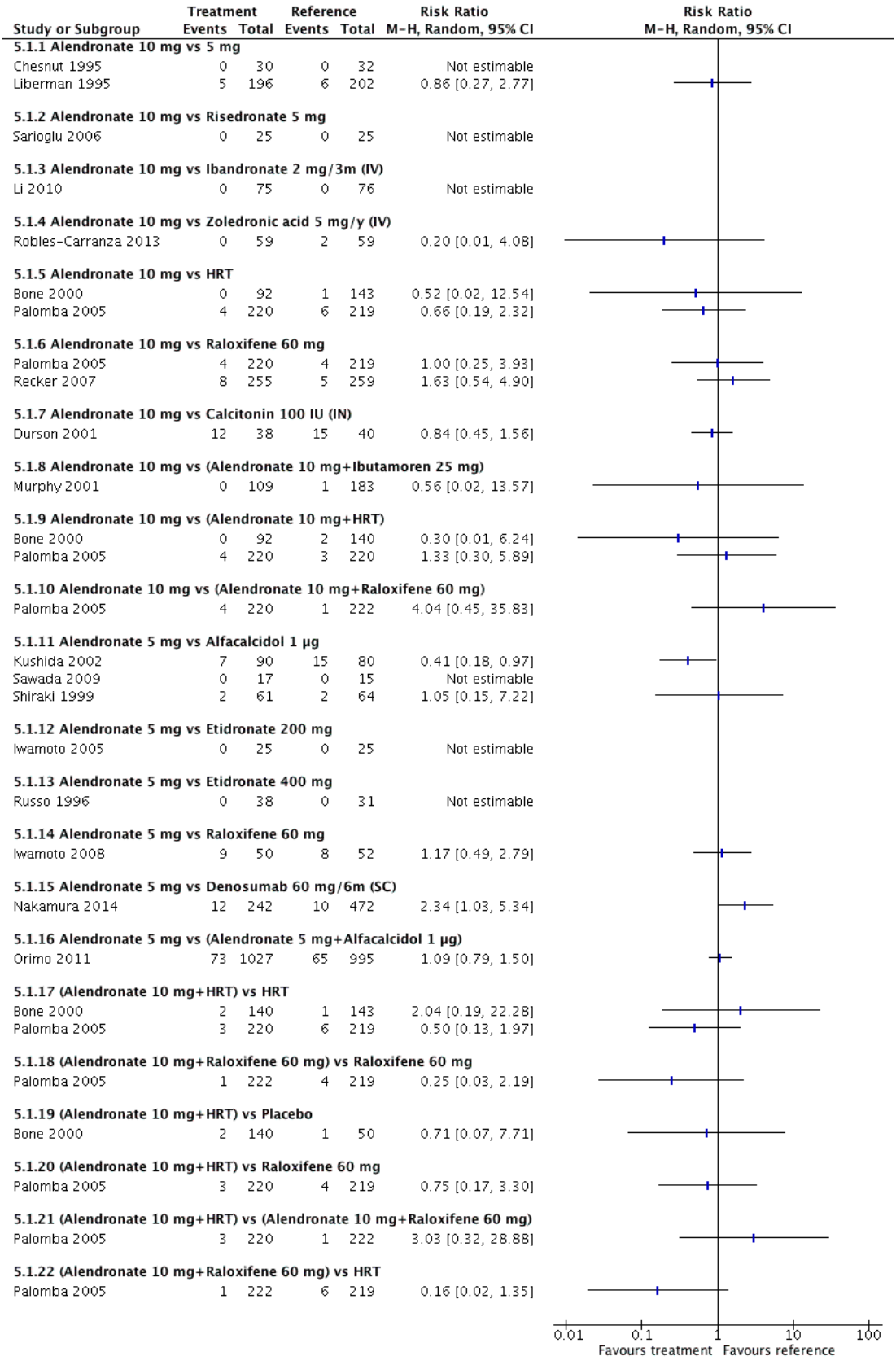


Figure 3.12: Alendronate versus active comparators or placebo, clinical vertebral fractures



3.3.5.2 SUBGROUP ANALYSES

None of the tests for subgroup differences were statistically significant (Figure 3.13). Secondary studies for the 10 mg dose showed a statistically significant risk reduction (RR 0.46, 95% CI: 0.28, 0.73) similar to the main analysis, while the primary prevention study showed no statistically significant difference between alendronate and placebo (RR 0.34, 95% CI: 0.01, 8.26). Alendronate had similar efficacy to placebo among two bisphosphonate-naïve trials and in the FLEX trial with bisphosphonate-experienced participants. Three years of treatment had the lowest effect estimate indicating a significant 55% reduction in risk of fracture compared to placebo (95% CI: 0.28, 0.73).

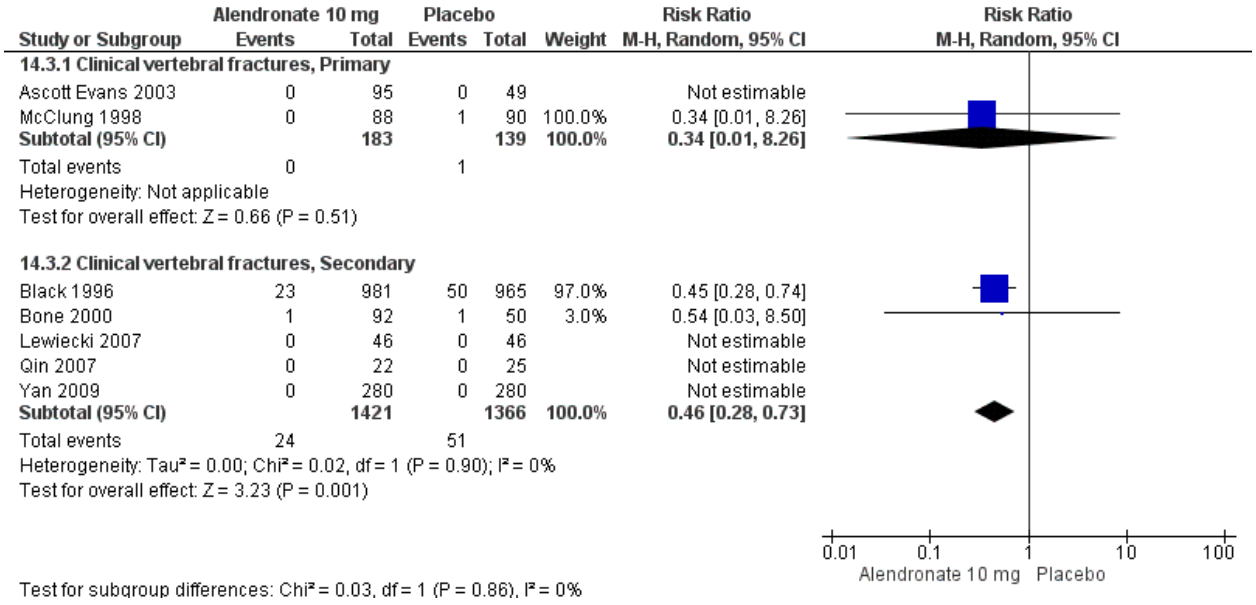
Among 5 mg/day studies, only one trial reported the occurrence of fractures (Figure 3.14). It is a primary prevention study with treatment duration of three years indicating no effect of alendronate 5 mg/day compared to placebo for clinical vertebral fractures (RR 1.02, 95% CI: 0.06, 16.10).

3.3.5.3 SENSITIVITY ANALYSES

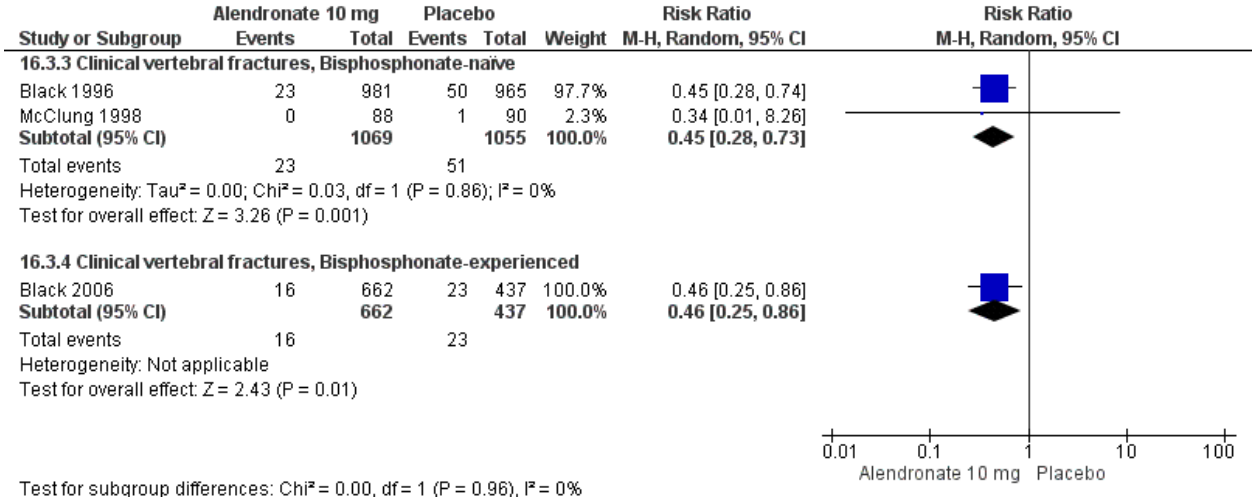
The change in threshold did not change estimates among 10 mg dose trials because only one study with zero events converted from secondary to primary prevention under the new criteria (96). Results from studies with low risk of bias, fracture as an efficacy outcome, or baseline denominators did not differ significantly from the main analyses.

Figure 3.13: Alendronate 10 mg versus placebo, clinical vertebral fractures (subgroup)

A) Primary or secondary prevention studies



B) Prior bisphosphonate experience



C) Treatment durations

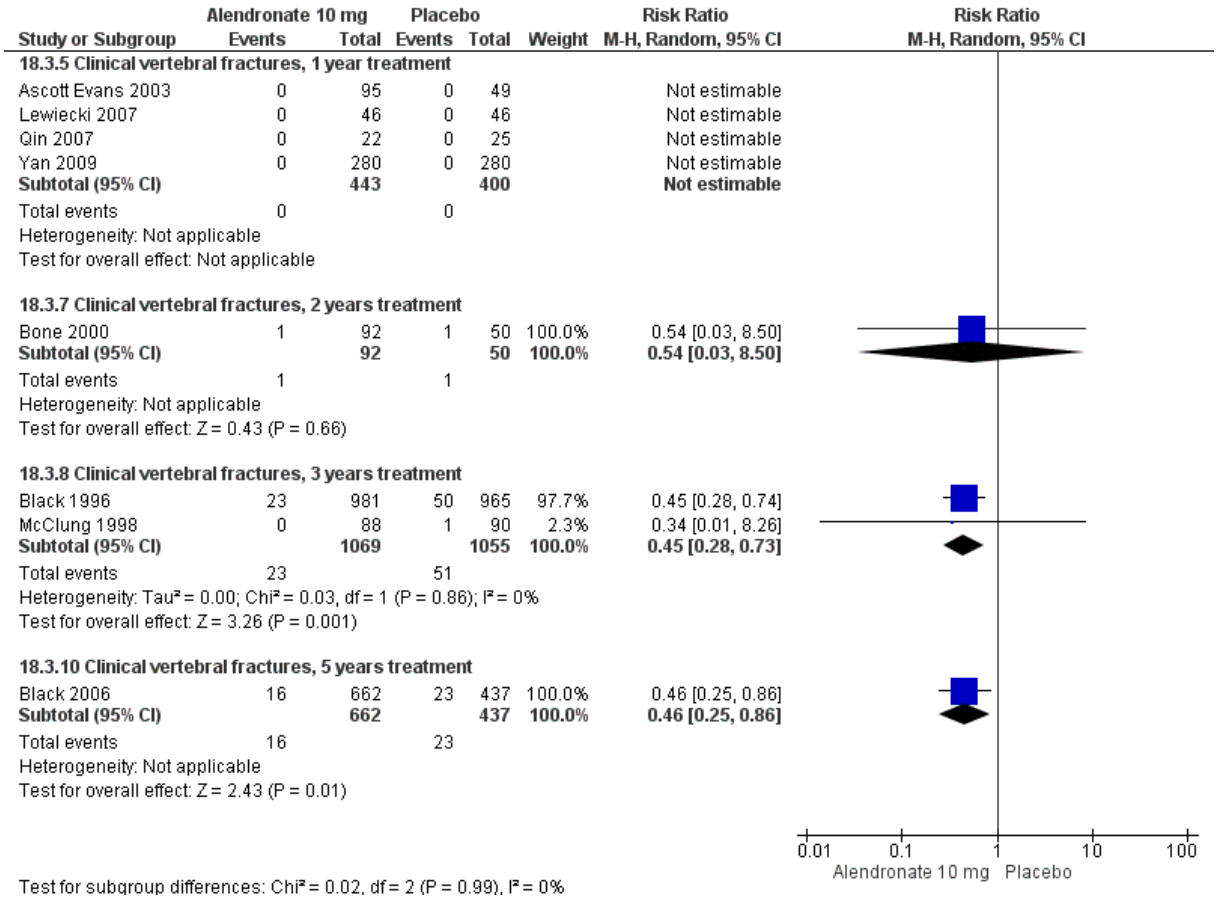


Figure 3.14: Alendronate 5 mg versus placebo, clinical vertebral fractures (subgroup)

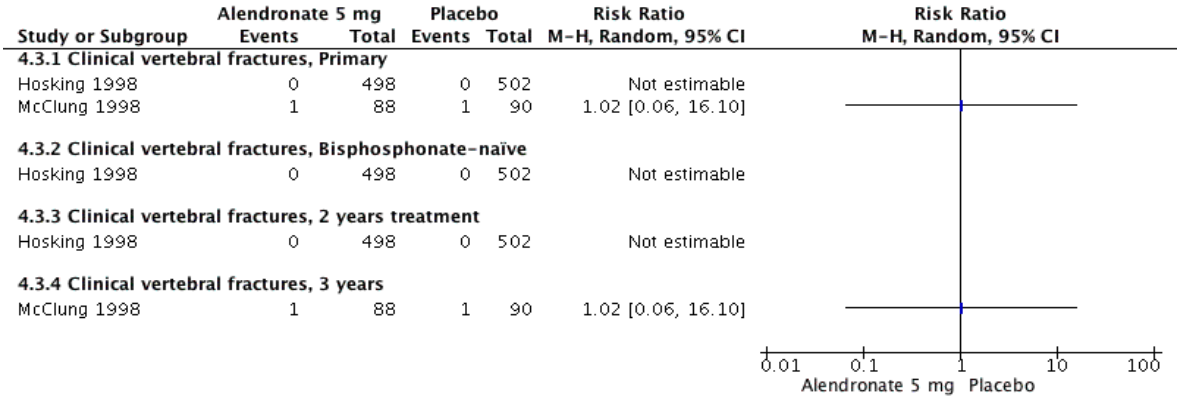
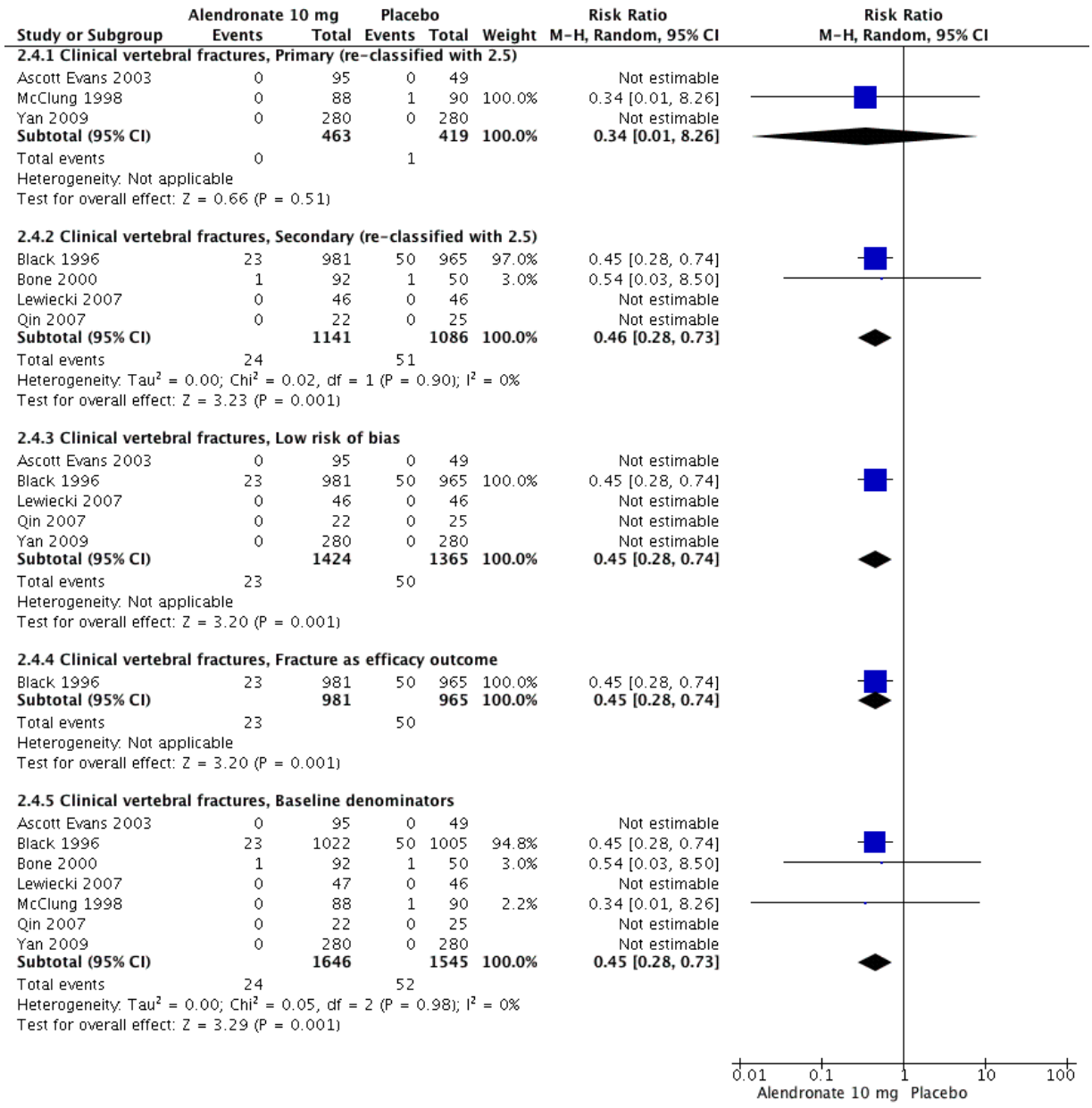


Figure 3.15: Alendronate 10 mg versus placebo, clinical vertebral fractures (sensitivity)



3.3.6 NON-VERTEBRAL FRACTURES

3.3.6.1 MAIN ANALYSIS

Women who received alendronate 10 mg/day had a statistically significant 17% reduction in risk of non-vertebral fracture compared to those who received placebo (95% CI: 0.73, 0.93). The reduction is 19% but not significant for 5 mg/day compared to placebo (95% CI: 0.45, 1.46). Eleven studies provided data for the 10 mg dose (total 10590 participants), and four studies provided data for the 5 mg dose (total 2084 participants). Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.18: alendronate versus an active or combination treatment (comparisons 7.1.1 to 7.1.18), alendronate combinations versus the same additional treatment (7.1.19 to 7.1.21), placebo (7.1.22) or a different treatment (7.1.23 to 7.1.27). These comparisons were not pooled for analysis due to varying comparators.

Figure 3.16: Alendronate 10 mg versus placebo, non-vertebral fractures

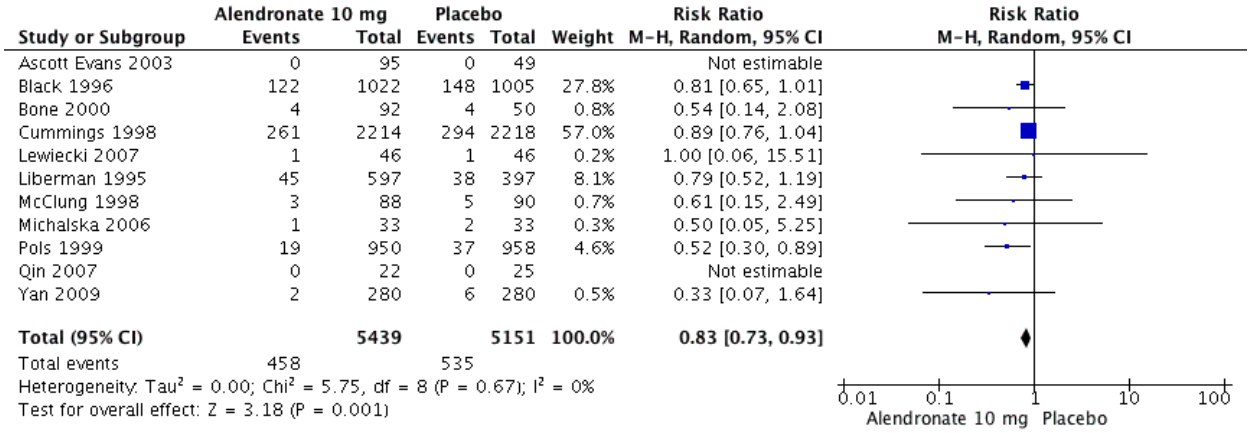


Figure 3.17: Alendronate 5 mg versus placebo, non-vertebral fractures

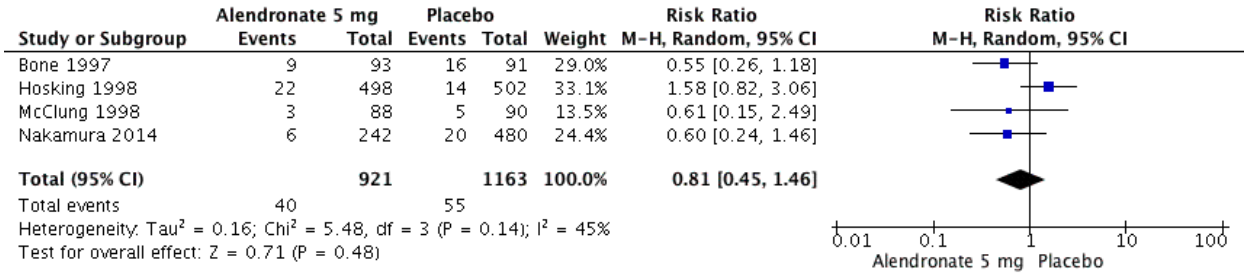
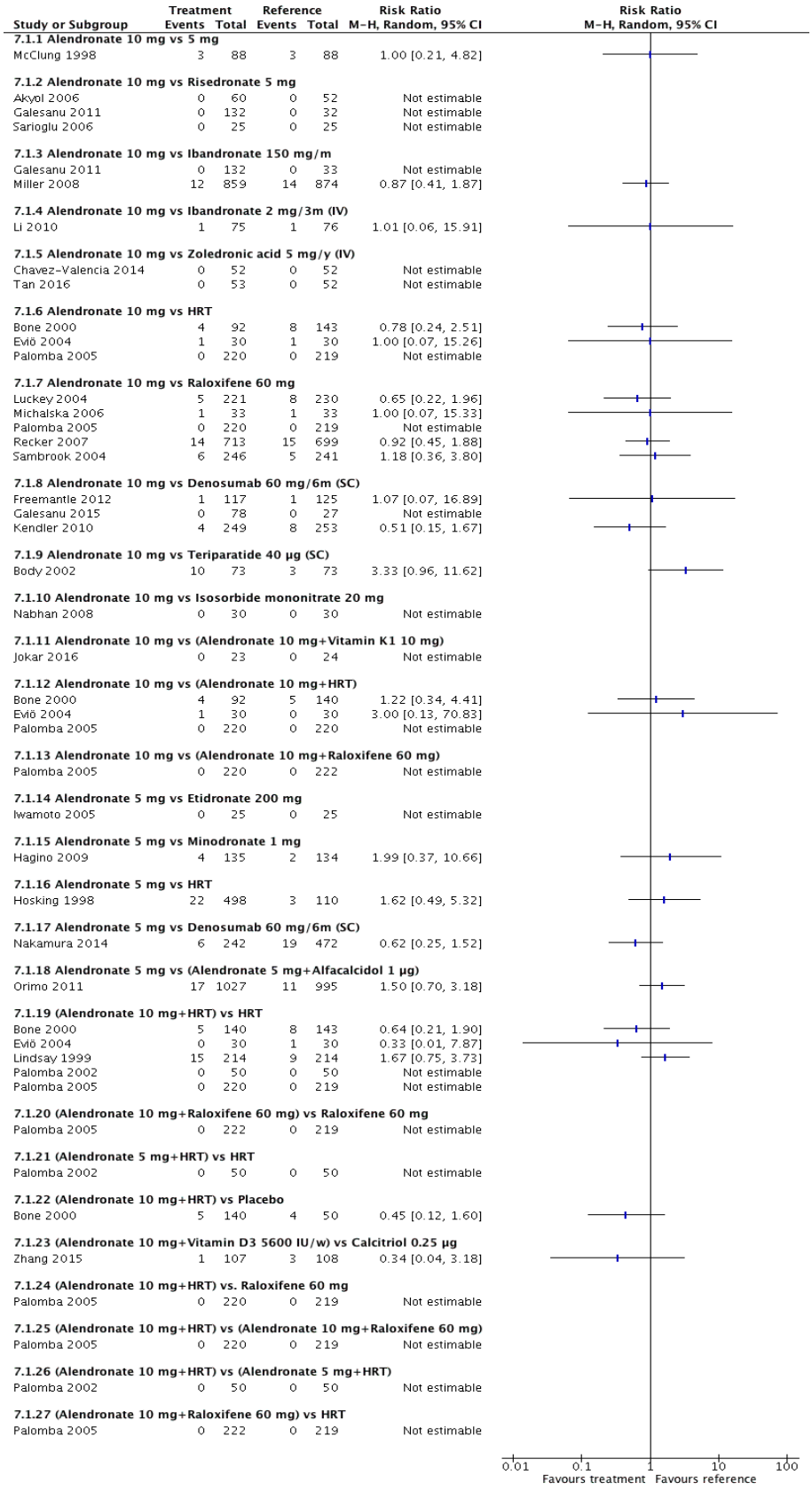


Figure 3.18: Alendronate versus active comparators or placebo, non-vertebral fractures



3.3.6.2 SUBGROUP ANALYSES

None of the tests for subgroup differences were statistically significant (Figure 3.19, 3.20). Alendronate 10 mg/day showed greater efficacy than placebo among secondary (RR 0.75, 95% CI: 0.63, 0.90) but not among primary prevention studies (RR 0.89, 95% CI: 0.76, 1.03). The 5 mg dose was not significantly better than placebo among main, primary or secondary analyses.

Among 10 mg/day comparisons, four trials with bisphosphonate-naïve participants had similar results to the main analysis, while two trials with bisphosphonate-experienced participants showed lower efficacy compared to the main analysis (RR 0.99, 95% CI: 0.77, 1.26). Only bisphosphonate-naïve studies were found for 5 mg trials and all showed similar efficacy to the main analysis.

Treatment durations ranged from one to five years among 10 mg/day dose comparisons and one to three years among 5 mg/day dose comparisons. Among studies with a 10 mg/day dose, only studies with data at two and three years of treatment showed significantly greater efficacy than placebo. In the 5 mg/day dose, only treatment at one year was significantly better than placebo. The significance at one year of treatment is attributed to the Vertebral Deformity Trial of FIT (86), where participants had a regimen of 5 mg/day during the first year and switched to alendronate 10 mg/day during subsequent years. The study dose was analyzed as 5 mg/day during the first year, and 10 mg/day during two and three years.

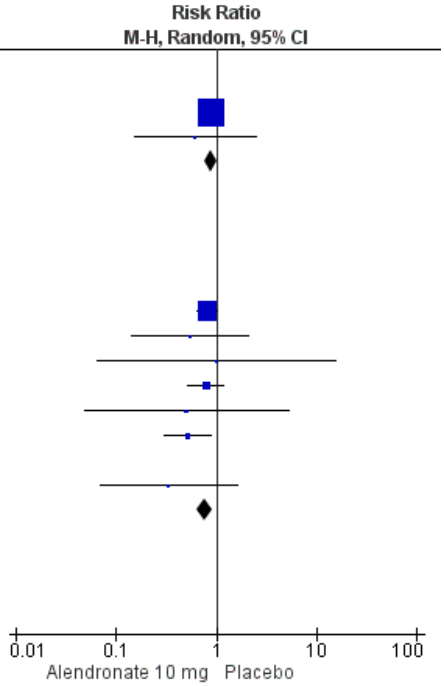
3.3.6.3 SENSITIVITY ANALYSES

Among studies comparing 10 mg/day to placebo, only one trial changed from secondary to primary prevention after re-classification (96). However, the risk ratio did not change substantially from analyses of primary and secondary prevention trials. No trial changed in classification among 5 mg/day dose studies. Results from sensitivity analyses on low risk of bias, fracture as an efficacy outcome, and baseline denominators did not show significant differences from the main analysis.

Figure 3.19: Alendronate 10 mg versus placebo, non-vertebral fractures (subgroup)

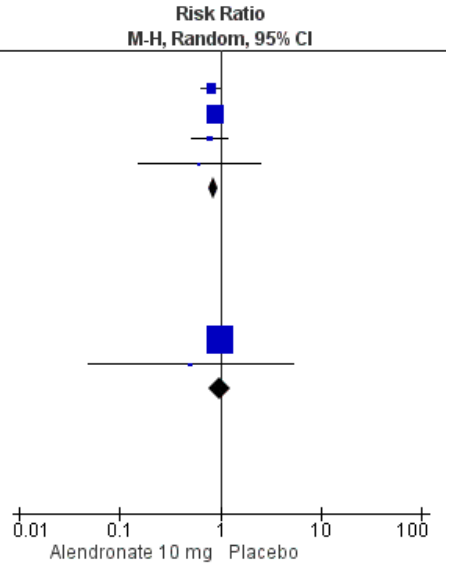
A) Primary or secondary prevention studies

Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.5.1 Non-vertebral fractures, Primary						
Ascott Evans 2003	0	95	0	49		Not estimable
Cummings 1998	261	2214	294	2218	98.8%	0.89 [0.76, 1.04]
McClung 1998	3	88	5	90	1.2%	0.61 [0.15, 2.49]
Subtotal (95% CI)		**2397**		**2357**	**100.0%**	**0.89 [0.76, 1.03]**
Total events	264		299			
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.54 (P = 0.12)						
14.5.2 Non-vertebral fractures, Secondary						
Black 1996	122	1022	148	1005	65.7%	0.81 [0.65, 1.01]
Bone 2000	4	92	4	50	1.8%	0.54 [0.14, 2.08]
Lewiecki 2007	1	46	1	46	0.4%	1.00 [0.06, 15.51]
Liberman 1995	45	597	38	397	19.2%	0.79 [0.52, 1.19]
Michalska 2006	1	33	2	33	0.6%	0.50 [0.05, 5.25]
Pols 1999	19	950	37	958	11.0%	0.52 [0.30, 0.89]
Qin 2007	0	22	0	25		Not estimable
Yan 2009	2	280	6	280	1.3%	0.33 [0.07, 1.64]
Subtotal (95% CI)		**3042**		**2794**	**100.0%**	**0.75 [0.63, 0.90]**
Total events	194		236			
Heterogeneity: Tau² = 0.00; Chi² = 3.68, df = 6 (P = 0.72); I² = 0%						
Test for overall effect: Z = 3.09 (P = 0.002)						
Test for subgroup differences: Chi² = 1.81, df = 1 (P = 0.18), I² = 44.8%						



B) Prior bisphosphonate experience

Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.5.3 Non-vertebral fractures, Bisphosphonate-naive						
Black 1996	122	1022	148	1005	29.7%	0.81 [0.65, 1.01]
Cummings 1998	261	2214	294	2218	60.9%	0.89 [0.76, 1.04]
Liberman 1995	45	597	38	397	8.7%	0.79 [0.52, 1.19]
McClung 1998	3	88	5	90	0.8%	0.61 [0.15, 2.49]
Subtotal (95% CI)		**3921**		**3710**	**100.0%**	**0.85 [0.76, 0.96]**
Total events	431		485			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.55 (P = 0.01)						
16.5.5 Non-vertebral fractures, Bisphosphonate-experienced						
Black 2006	125	662	83	437	98.9%	0.99 [0.77, 1.28]
Michalska 2006	1	33	2	33	1.1%	0.50 [0.05, 5.25]
Subtotal (95% CI)		**695**		**470**	**100.0%**	**0.99 [0.77, 1.26]**
Total events	126		85			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.7%						



C) Treatment durations

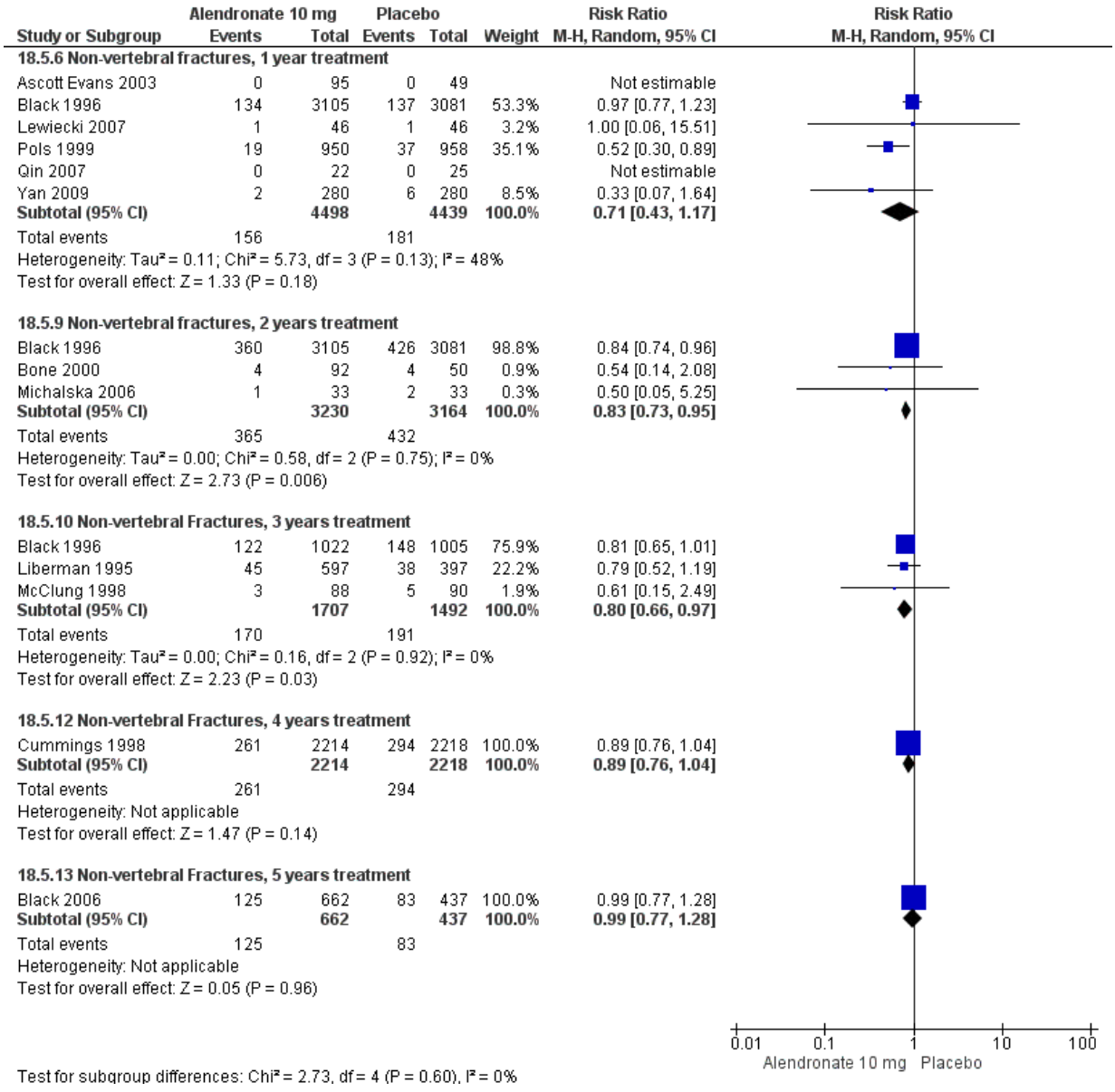
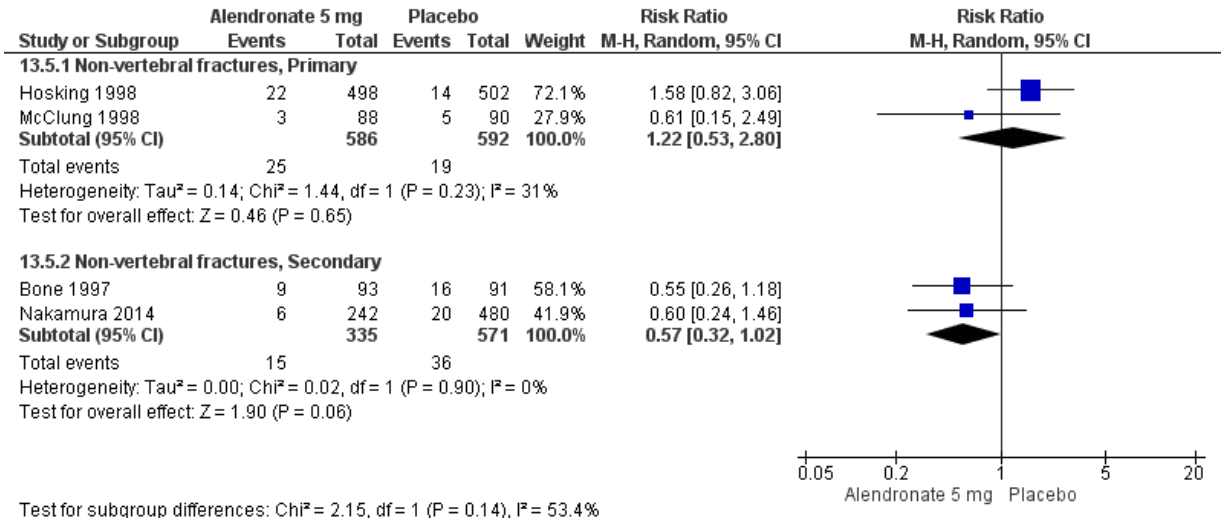
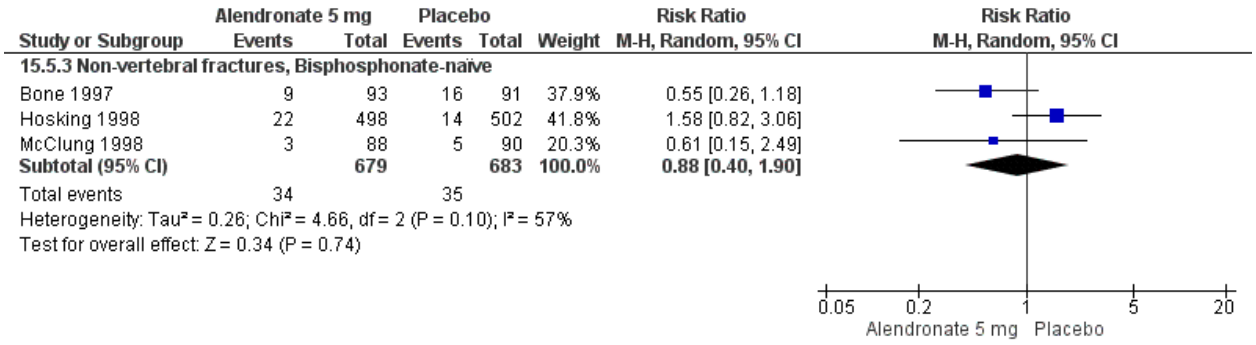


Figure 3.20: Alendronate 5 mg versus placebo, non-vertebral fractures (subgroup)

A) Primary or secondary prevention studies

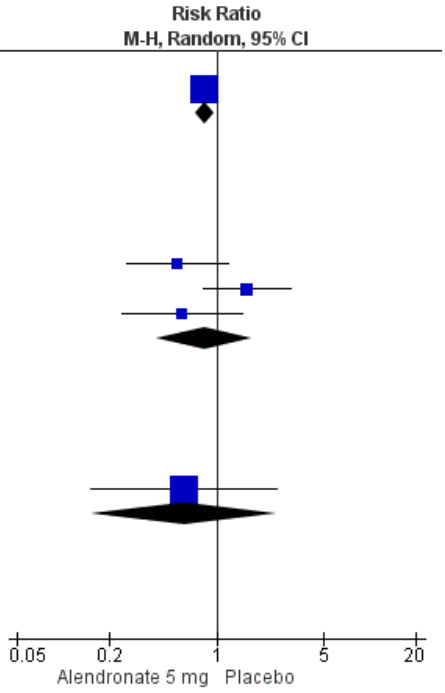


B) Prior bisphosphonate experience



C) Treatment durations

Study or Subgroup	Alendronate 5 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.5.4 Non-vertebral fractures, 1 year treatment						
Black 1996	360	3105	426	3081	100.0%	0.84 [0.74, 0.96]
Subtotal (95% CI)		**3105**		**3081**	**100.0%**	**0.84 [0.74, 0.96]**
Total events	360		426			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
17.5.5 Non-vertebral fractures, 2 years treatment						
Bone 1997	9	93	16	91	33.6%	0.55 [0.26, 1.18]
Hosking 1998	22	498	14	502	37.2%	1.58 [0.82, 3.06]
Nakamura 2014	6	242	20	480	29.3%	0.60 [0.24, 1.46]
Subtotal (95% CI)		**833**		**1073**	**100.0%**	**0.83 [0.41, 1.71]**
Total events	37		50			
Heterogeneity: Tau² = 0.25; Chi² = 5.24, df = 2 (P = 0.07); I² = 62%						
Test for overall effect: Z = 0.49 (P = 0.62)						
17.5.7 Non-vertebral Fractures, 3 years treatment						
McClung 1998	3	88	5	90	100.0%	0.61 [0.15, 2.49]
Subtotal (95% CI)		**88**		**90**	**100.0%**	**0.61 [0.15, 2.49]**
Total events	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.49)						



Test for subgroup differences: Chi² = 0.19, df = 2 (P = 0.91), I² = 0%

Figure 3.21: Alendronate 10 mg versus placebo, non-vertebral fractures (sensitivity)

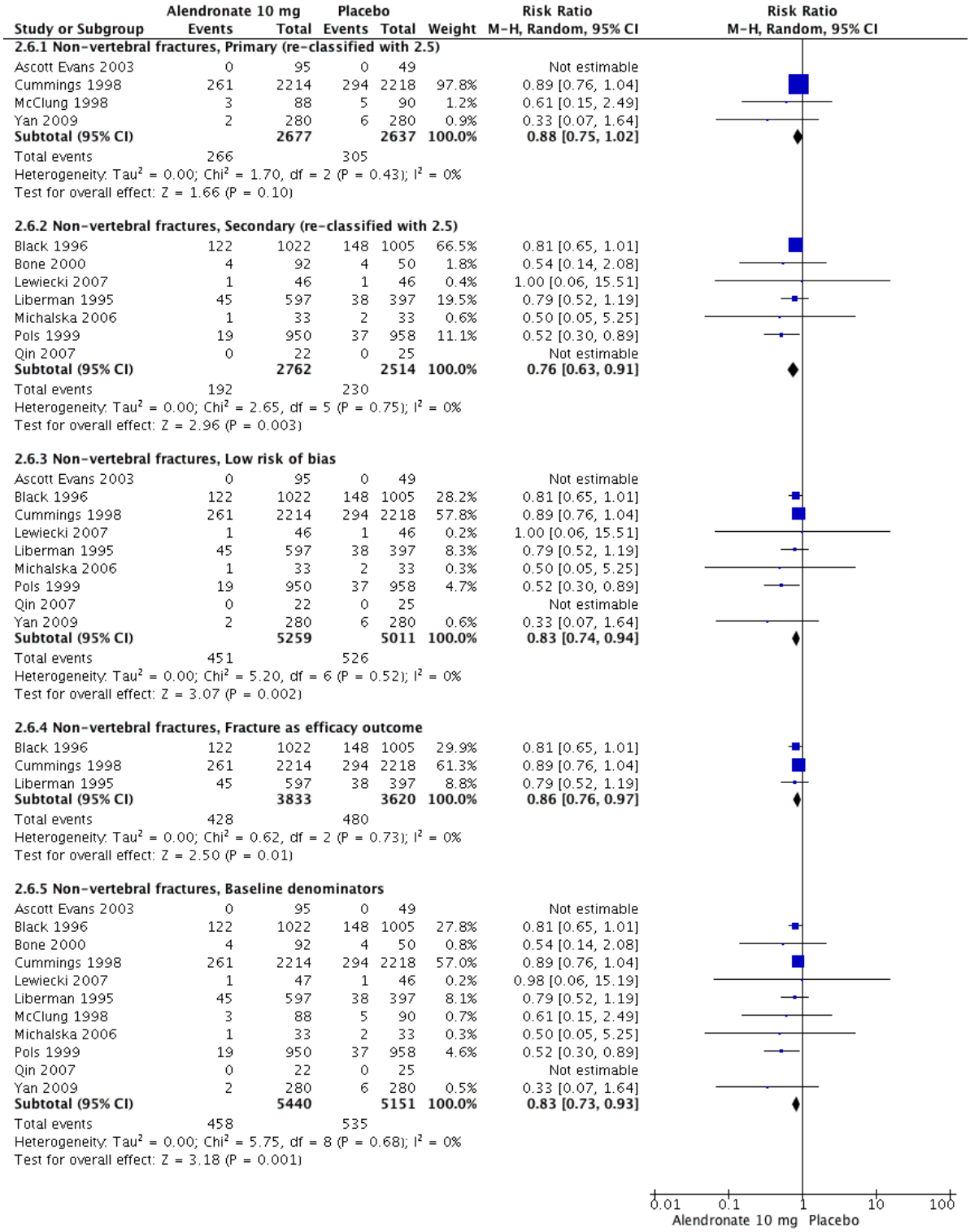
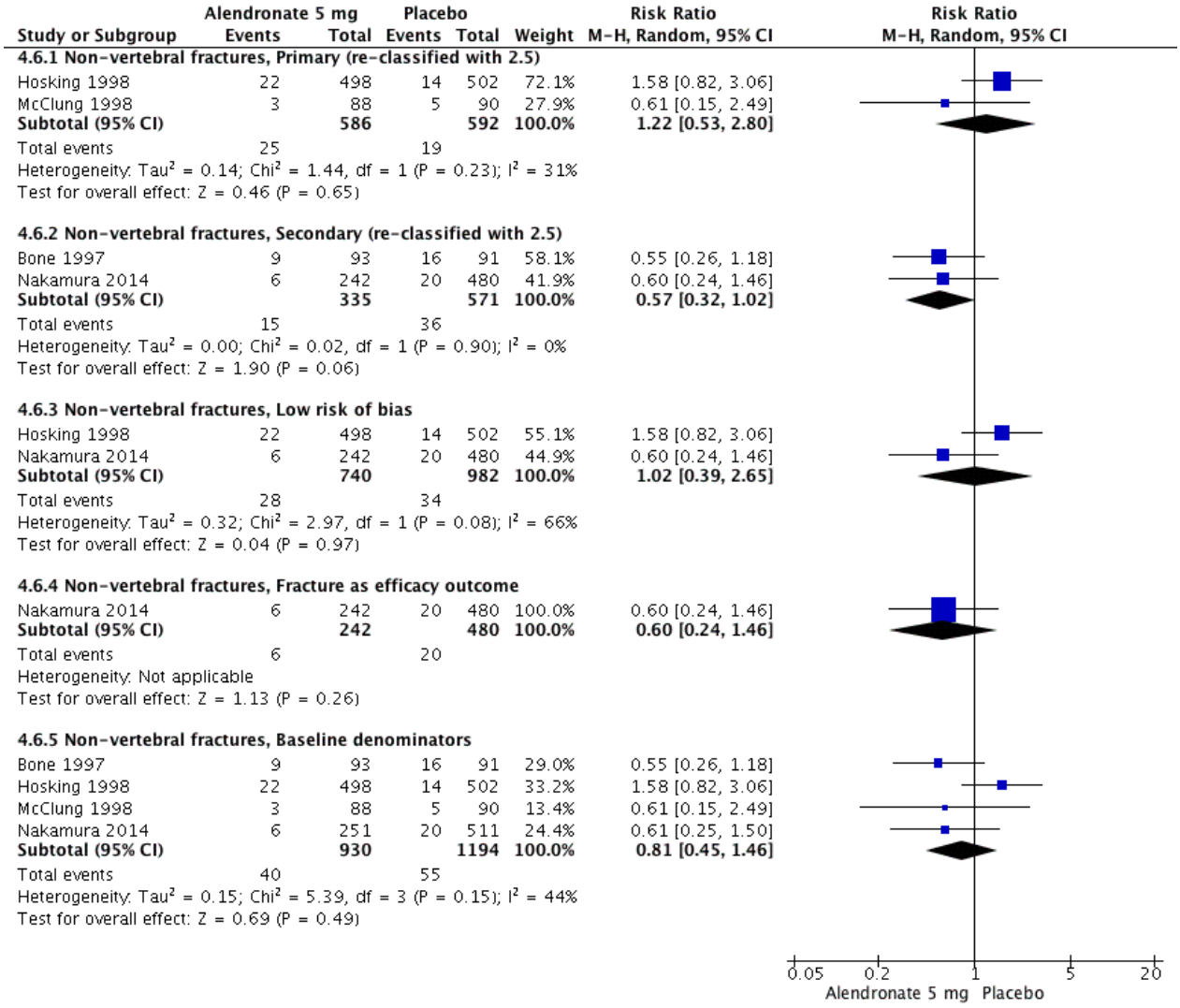


Figure 3.22: Alendronate 5 mg versus placebo, non-vertebral fractures (sensitivity)



3.3.7 HIP FRACTURES

3.3.7.1 MAIN ANALYSIS

Women who received alendronate 10 mg/day had a statistically significant 39% risk reduction of hip fracture compared to those who received placebo (95% CI: 0.49, 1.00), while the reduction is 60% but not statistically significant for 5 mg/day compared to placebo (95% CI: 0.02, 8.21). Eleven studies provided data for the 10 mg dose (total 10793 participants), and one study provided data for the 5 mg dose (total 722 participants). Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.25: alendronate alone versus an active or combination treatment (comparisons 5.1.1 to 5.1.16), alendronate combinations versus the same treatment (5.1.17 to 5.1.18), placebo (5.1.19), or a different drug (5.1.20 to 5.1.22).

Figure 3.23: Alendronate 10 mg versus placebo, hip fractures

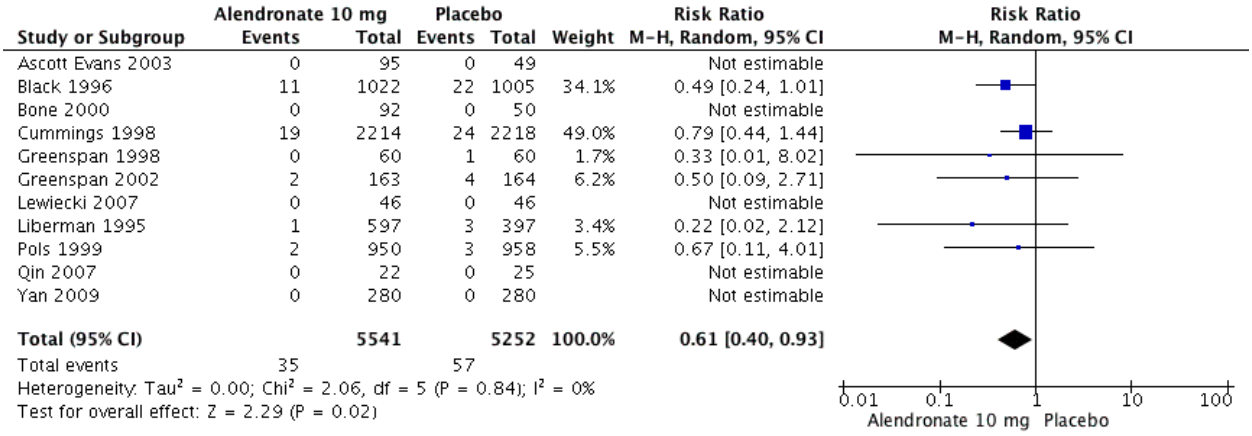


Figure 3.24: Alendronate 5 mg versus placebo, hip fractures

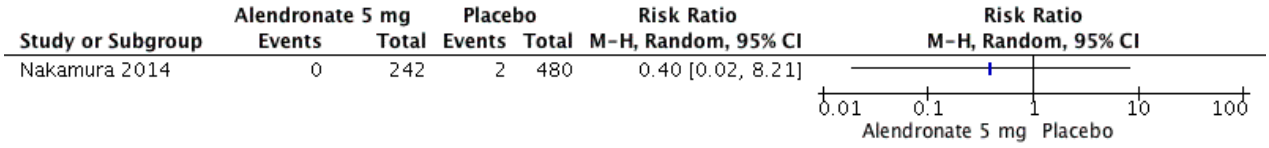
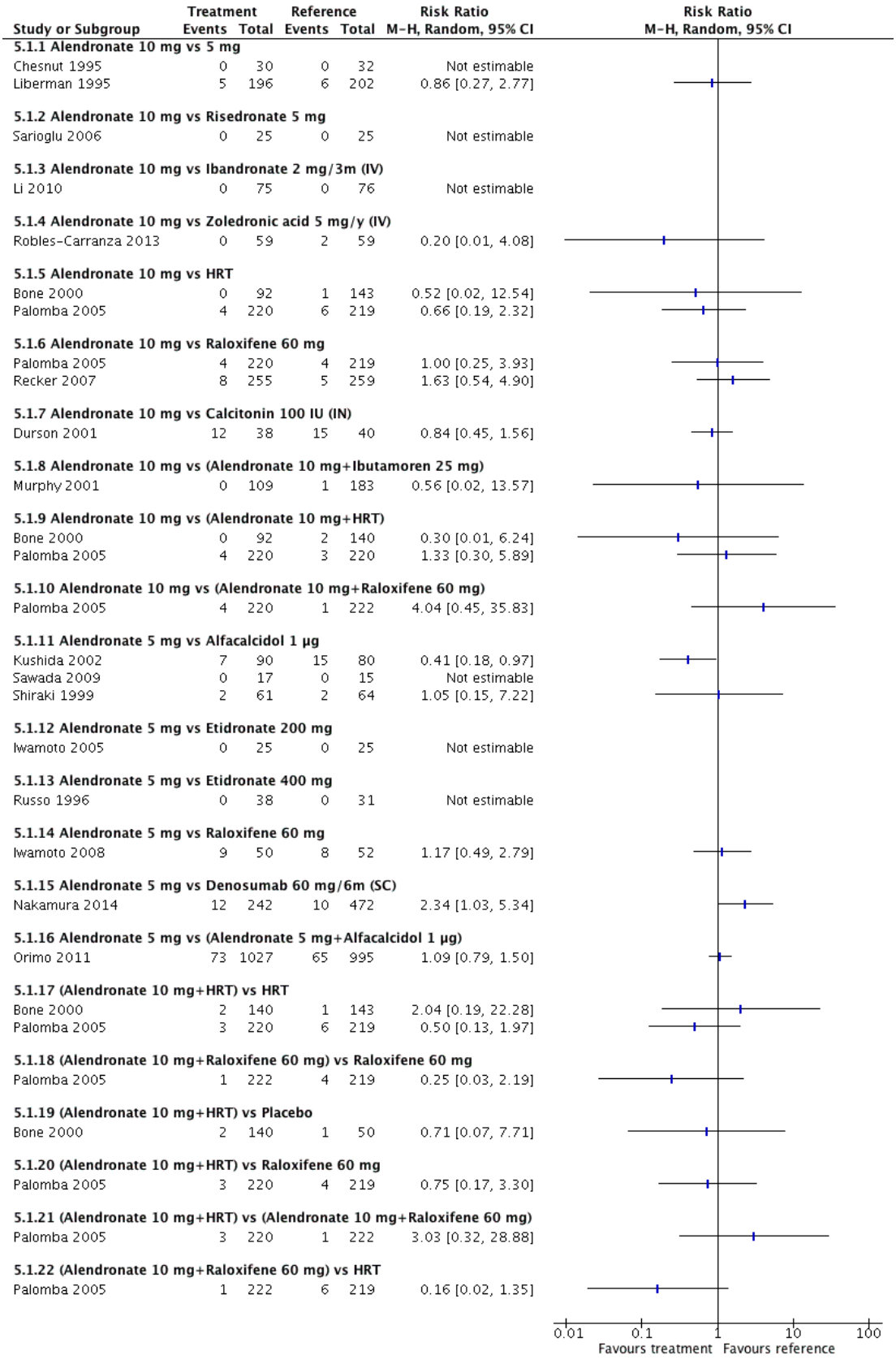


Figure 3.25: Alendronate versus active comparators or placebo, hip fractures



3.3.7.2 SUBGROUP ANALYSES

No statistically significant differences were found between any of the subgroups (Figure 3.26). A statistically significant risk reduction was found in participants taking alendronate compared to placebo among five secondary prevention studies (RR 0.48, 95% CI: 0.27, 0.86) but not in the only primary prevention study (RR 0.79, 95% CI: 0.44, 1.44). Four trials with bisphosphonate-naïve participants showed a significant 38% reduction in risk compared to placebo (95% CI: 0.39, 0.96), but not in the FLEX trial with bisphosphonate-experienced participants.

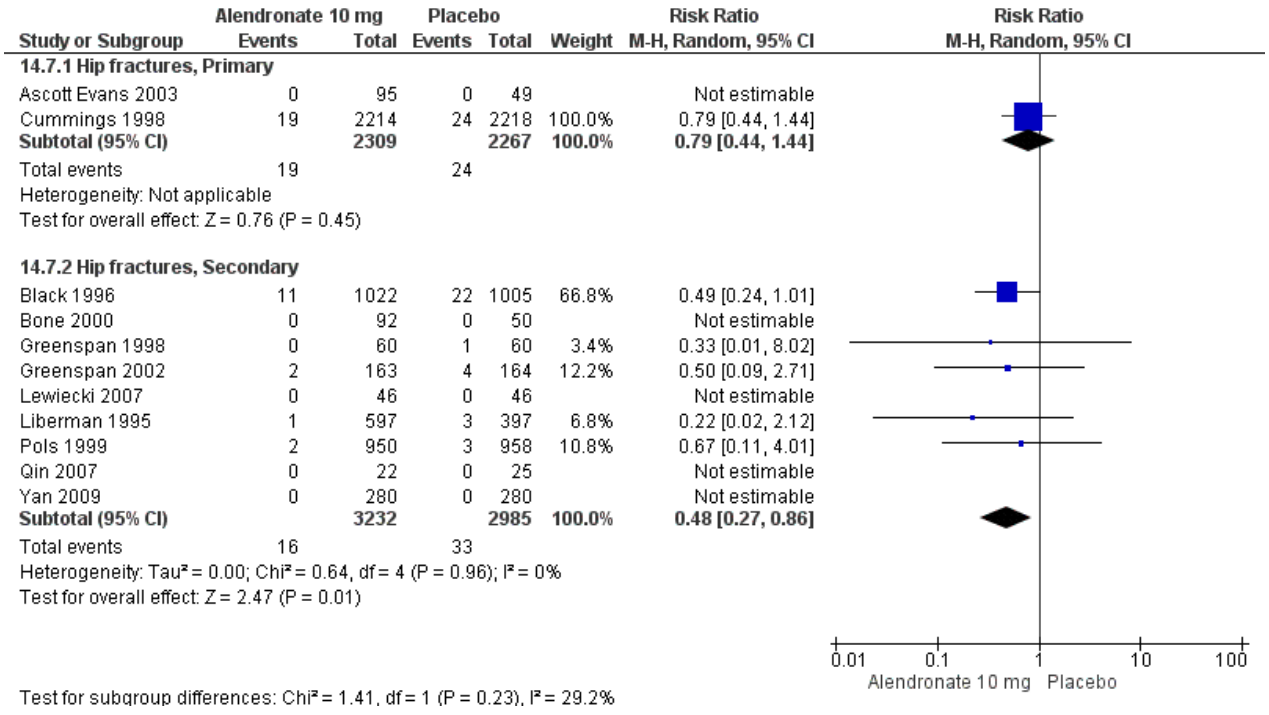
Alendronate had a statistically significant risk reduction compared to placebo at three years of treatment (RR 0.45, 95% CI: 0.23, 0.88). Only one study was included that compared alendronate 5 mg/day to placebo (84), a secondary prevention study with two years of treatment that did not show a significant difference between treatments (RR 0.40, 95% CI: 0.02, 8.21).

3.3.7.3 SENSITIVITY ANALYSES

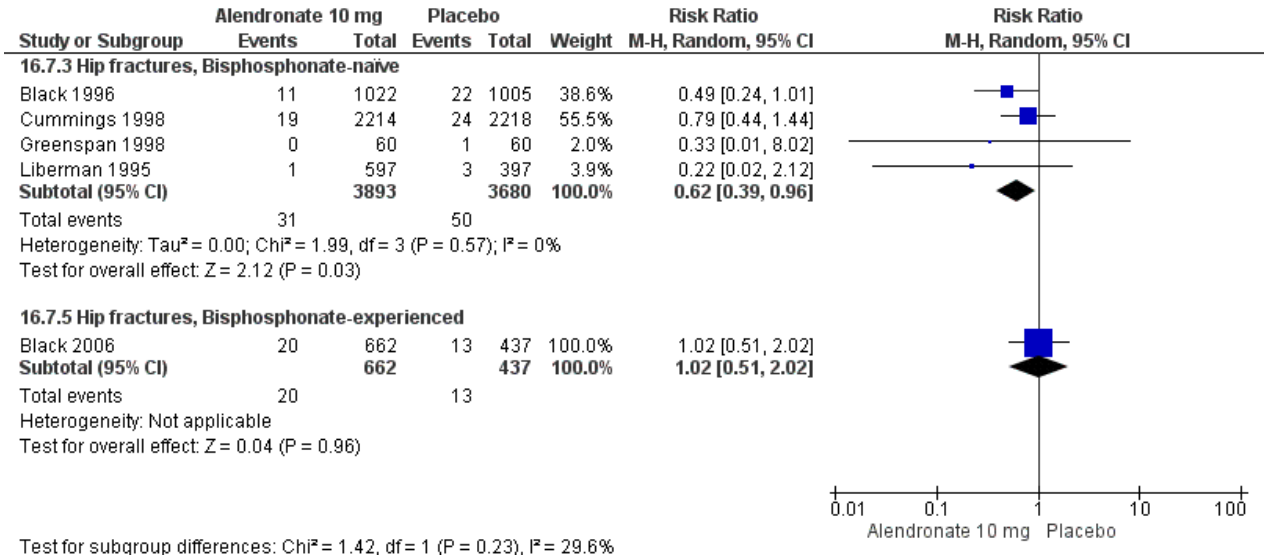
Although one study changed from secondary to primary prevention after re-classification (96), this did not impact the analysis of alendronate 10 mg/day versus placebo because the trial had zero events in all arms. Results from sensitivity analyses on low risk of bias and baseline denominators showed no substantial differences from the main analysis. Among two studies with fracture as an efficacy outcome, alendronate 10 mg/day had a statistically significant 54% reduction in risk of hip fracture compared to placebo (95% CI: 0.23, 0.91). Only one study assessed alendronate 5 mg/day versus placebo for hip fracture.

Figure 3.26: Alendronate 10 mg versus placebo, hip fractures (subgroup)

A) Primary or secondary prevention studies



B) Prior bisphosphonate experience



C) Treatment durations

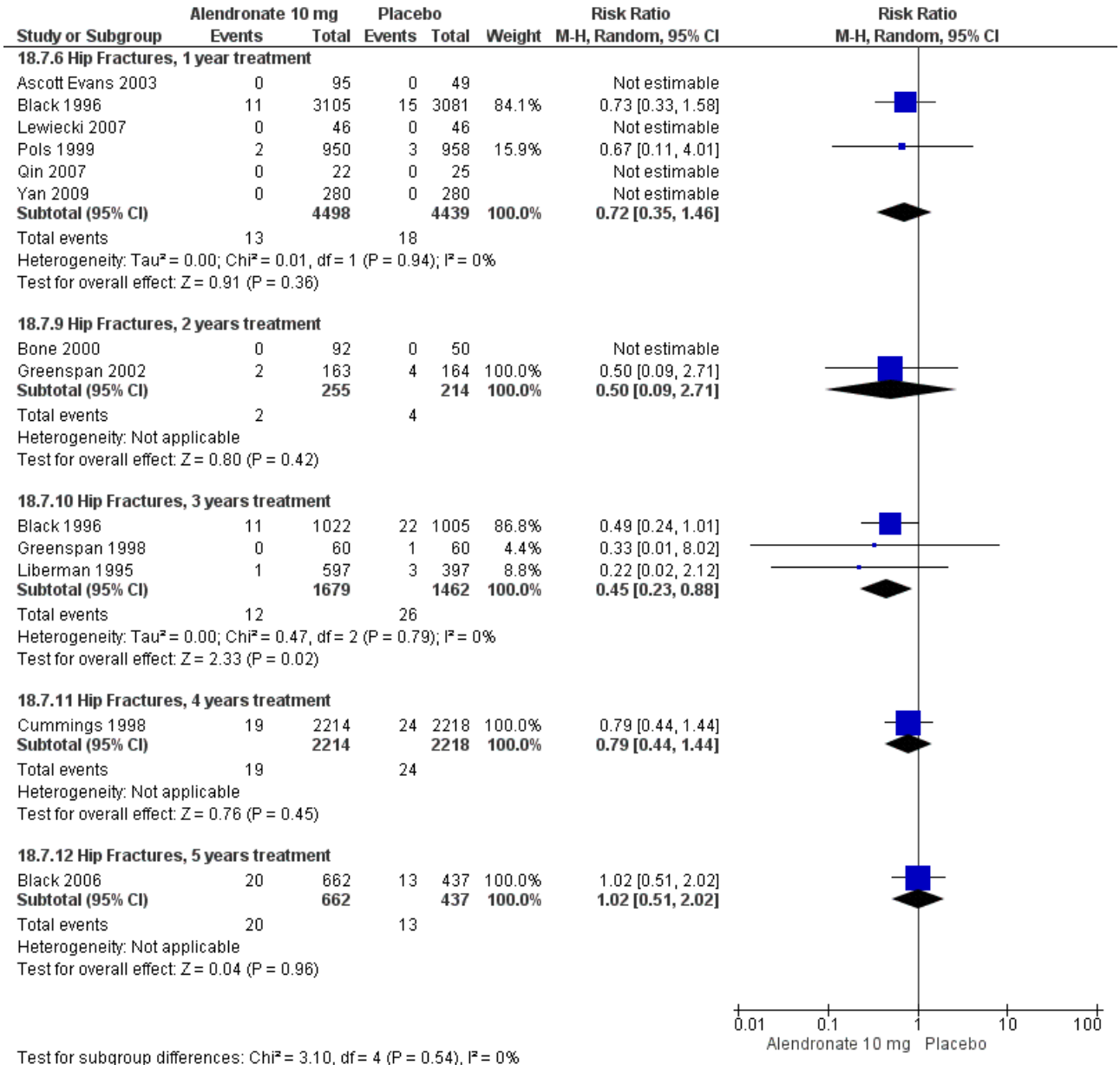
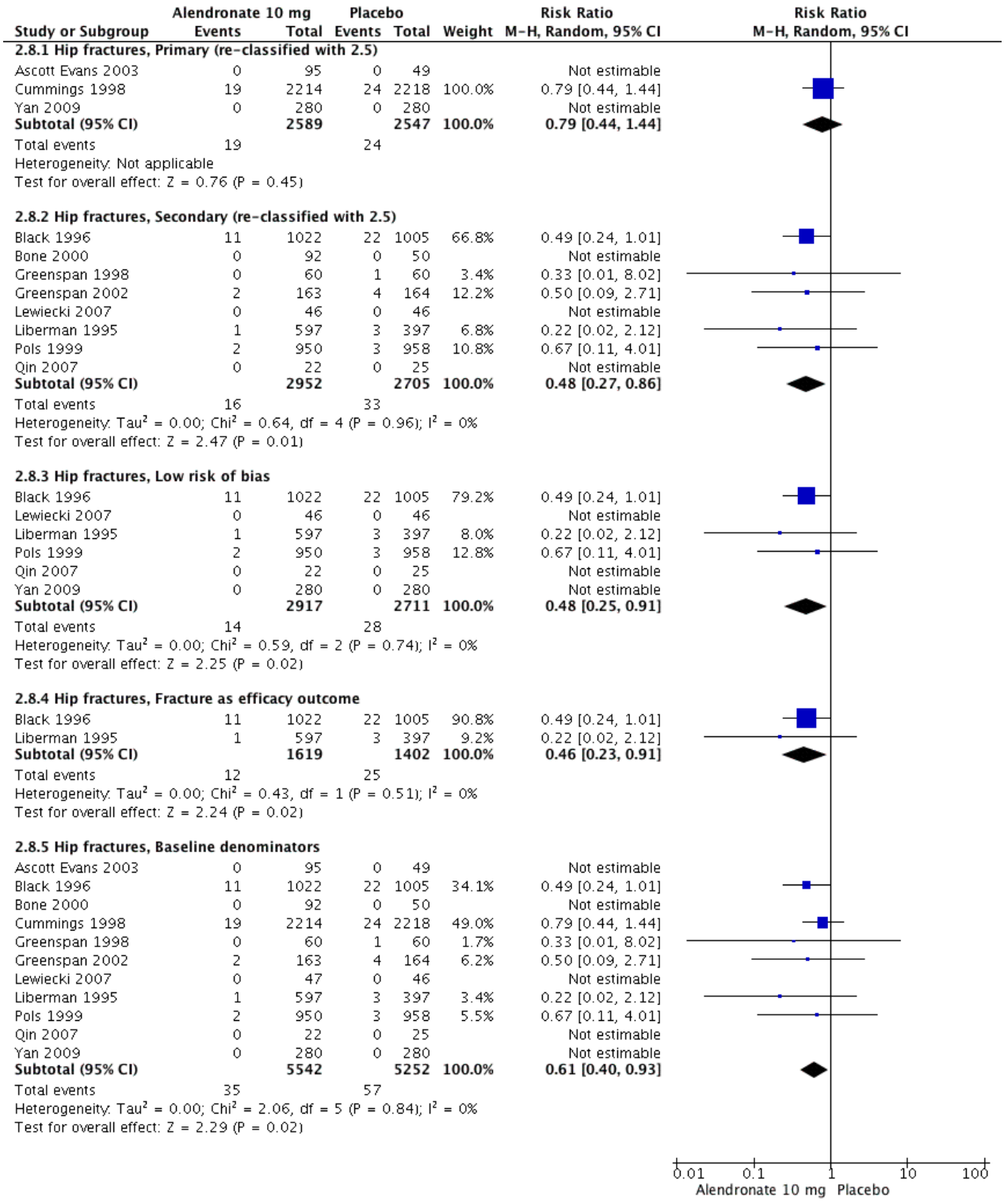


Figure 3.27: Alendronate 10 mg versus placebo, hip fractures (sensitivity)



3.3.8 WRIST FRACTURES

3.3.8.1 MAIN ANALYSIS

Women who received alendronate 10 mg/day had a statistically non-significant 18% lower risk of sustaining a hip fracture compared to those who received placebo (95% CI: 0.44, 1.54). The effect was not estimable for the 5 mg/day dose. Nine studies provided data for the 10 mg dose (total 9090 participants), one study provided data for the 5 mg dose (total 178 participants) with zero fractures in all arms. Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.30: alendronate versus active treatments or combinations (comparisons 9.1.1 to 9.1.17), alendronate combination versus same treatment (9.1.18 to 9.1.20), placebo (9.1.21), or a different treatment (9.1.22 to 9.1.26).

Figure 3.28: Alendronate 10 mg versus placebo, wrist fractures

Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ascott Evans 2003	0	95	0	49		Not estimable
Black 1996	22	1022	41	1005	31.6%	0.53 [0.32, 0.88]
Bone 2000	1	92	0	50	3.5%	1.65 [0.07, 39.65]
Cummings 1998	83	2214	70	2218	36.4%	1.19 [0.87, 1.62]
Greenspan 1998	3	60	0	60	4.1%	7.00 [0.37, 132.66]
Lewiecki 2007	0	46	0	46		Not estimable
McClung 1998	1	88	0	90	3.5%	3.07 [0.13, 74.30]
Pols 1999	6	950	15	958	21.0%	0.40 [0.16, 1.04]
Qin 2007	0	22	0	25		Not estimable
Total (95% CI)		**4589**		**4501**	**100.0%**	**0.82 [0.44, 1.54]**
Total events	116		126			

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 12.57$, df = 5 (P = 0.03); $I^2 = 60\%$
Test for overall effect: Z = 0.61 (P = 0.54)

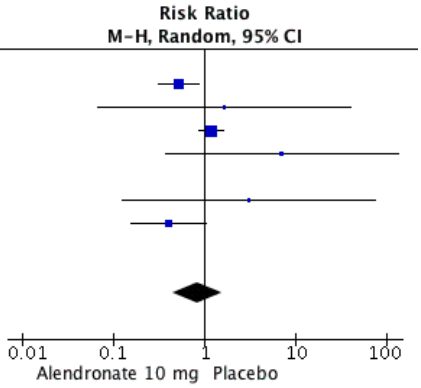


Figure 3.29: Alendronate 5 mg versus placebo, wrist fractures

Study or Subgroup	Alendronate 5 mg Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
McClung 1998	0	88	0	90	Not estimable

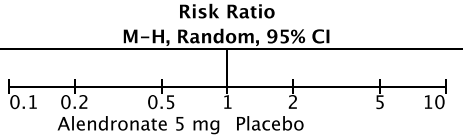
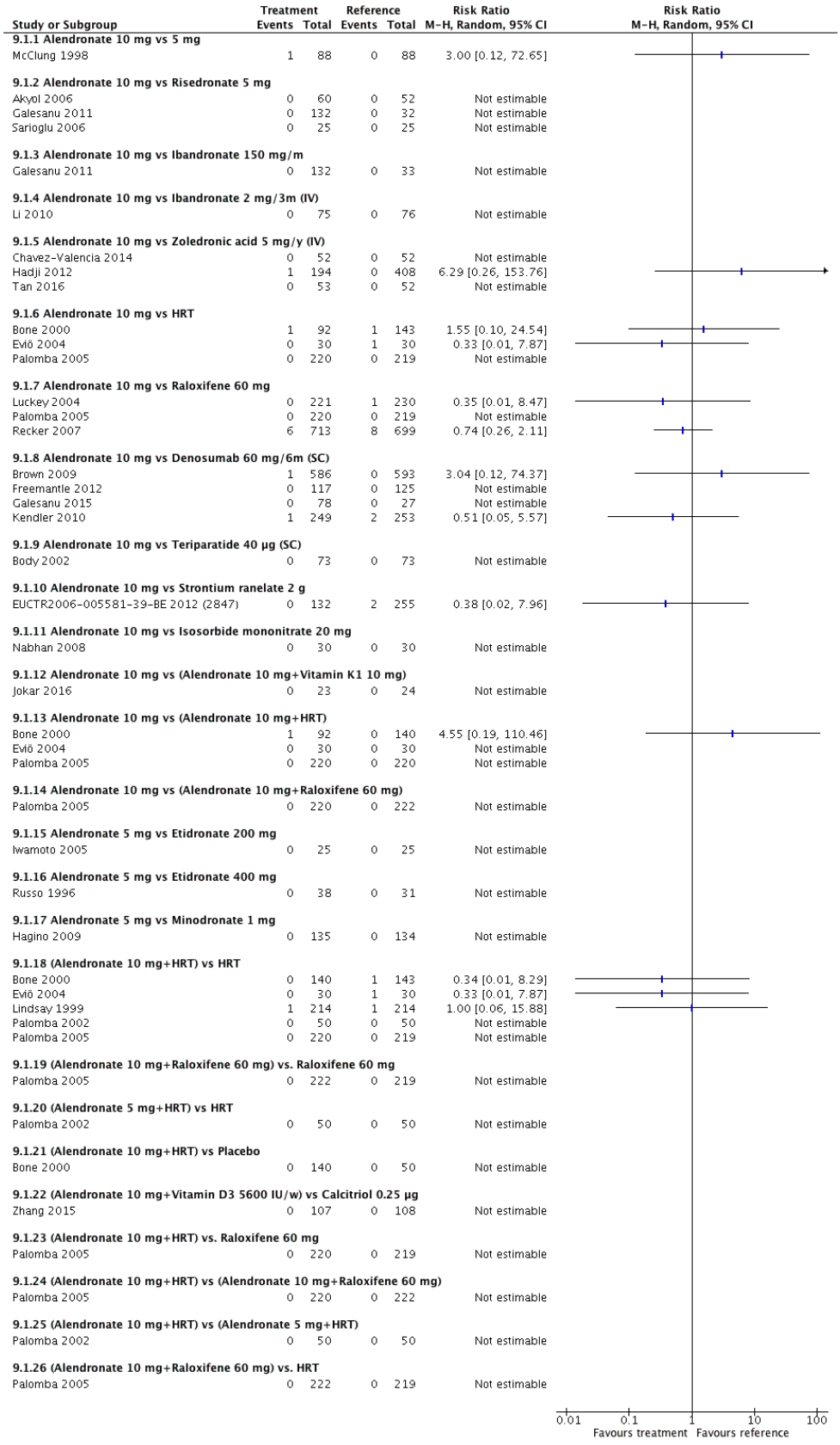


Figure 3.30: Alendronate versus active comparators or placebo, wrist fractures



3.3.8.2 SUBGROUP ANALYSES

Results from subgroups of primary and secondary prevention studies indicate no greater efficacy of alendronate compared to placebo, although the relative risk estimate for secondary prevention studies indicate a statistically non-significant 43% reduction in relative risk (primary prevention RR 1.20, 95% CI: 0.88, 1.64; secondary prevention RR 0.57, 95% CI: 0.30, 1.06). However, the test for subgroup differences was statistically significant between primary and secondary prevention studies (p=0.04) and substantial heterogeneity was found in the 10 mg comparison to placebo (I^2=77%, Figure 3.31). While there was no detectable heterogeneity within primary prevention studies (I^2=0%), there was a low level of heterogeneity found among secondary prevention studies (I^2=21%). The estimates by two larger trials, Black et al. (1996) and Pols et al. (1999) tend to favour alendronate with narrower confidence intervals, while results of the two smaller trials by Bone et al. (2000) and Greenspan et al. (1998) tend to favour placebo with wide confidence intervals. The trials by Bone et al. (2000) and Greenspan et al. (1998) had 4 events total with small sample sizes (n=262 combined), thus the differences in effect estimates may be due to chance.

Only the Vertebral Fracture trial of FIT qualified as a bisphosphonate-naïve study, showing a statistically significant reduction in fracture risk compared to placebo (RR 0.53, 95% CI: 0.32, 0.88). No bisphosphonate-experienced studies were found.

Treatment durations ranged from one to four years. No statistically significant subgroup difference was found between the any of the treatment durations for wrist fracture prevention.

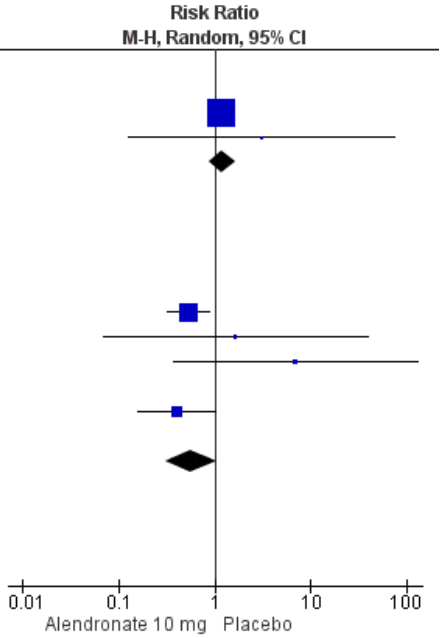
No subgroup analysis was conducted for the 5 mg dose because only one study was included with zero fractures in all arms.

Figure 3.31: Alendronate 10 mg versus placebo, wrist fractures (subgroup)

A) Primary or secondary prevention studies

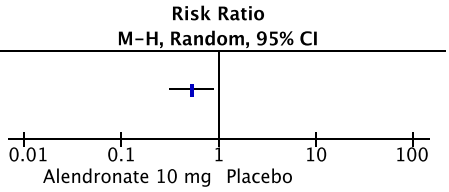
Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.9.1 Wrist fractures, Primary						
Ascott Evans 2003	0	95	0	49		Not estimable
Cummings 1998	83	2214	70	2218	99.0%	1.19 [0.87, 1.62]
McClung 1998	1	88	0	90	1.0%	3.07 [0.13, 74.30]
Subtotal (95% CI)		**2397**		**2357**	**100.0%**	**1.20 [0.88, 1.64]**
Total events	84		70			
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.25)						
14.9.2 Wrist fractures, Secondary						
Black 1996	22	1022	41	1005	61.0%	0.53 [0.32, 0.88]
Bone 2000	1	92	0	50	3.7%	1.65 [0.07, 39.65]
Greenspan 1998	3	60	0	60	4.4%	7.00 [0.37, 132.66]
Lewiecki 2007	0	46	0	46		Not estimable
Pols 1999	6	950	15	958	30.9%	0.40 [0.16, 1.04]
Qin 2007	0	22	0	25		Not estimable
Subtotal (95% CI)		**2192**		**2144**	**100.0%**	**0.57 [0.30, 1.06]**
Total events	32		56			
Heterogeneity: Tau² = 0.10; Chi² = 3.80, df = 3 (P = 0.28); I² = 21%						
Test for overall effect: Z = 1.77 (P = 0.08)						

Test for subgroup differences: Chi² = 4.39, df = 1 (P = 0.04), I² = 77.2%

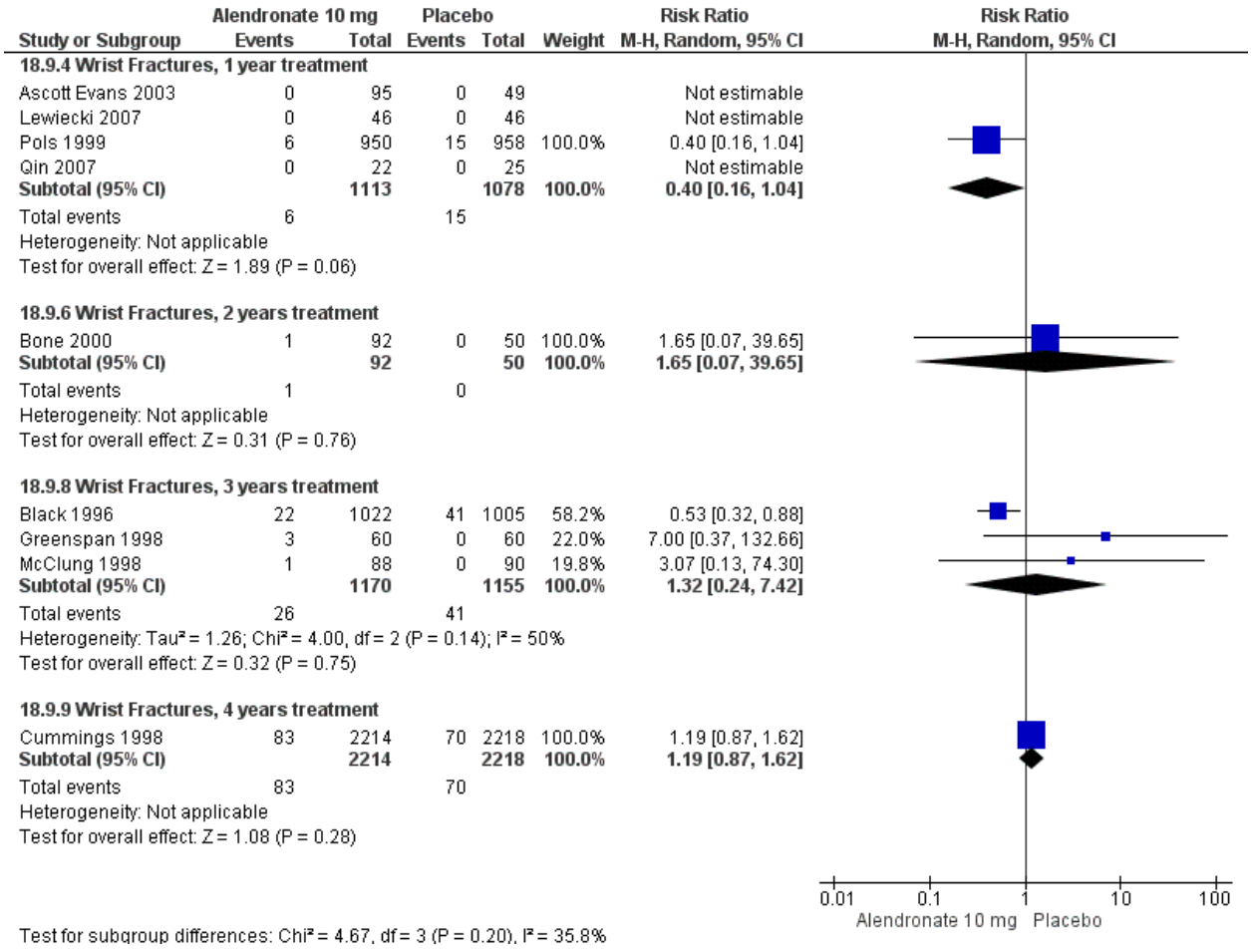


B) Prior bisphosphonate experience

Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
16.9.3 Wrist fractures, Bisphosphonate-naïve					
Black 1996	22	1022	41	1005	0.53 [0.32, 0.88]



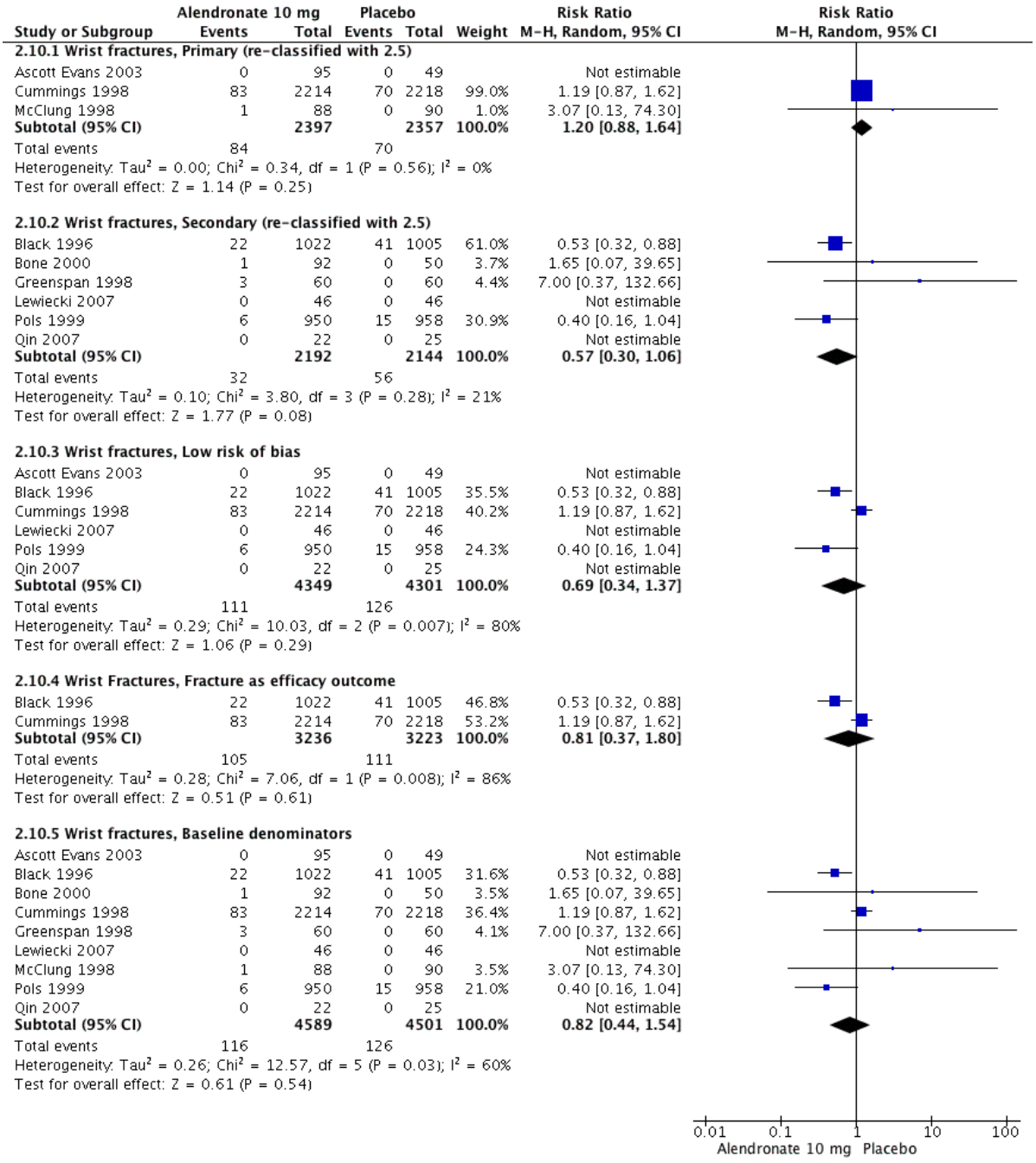
C) Treatment durations



3.3.8.3 SENSITIVITY ANALYSES

No studies changed in prevention type after re-classification using 2.5 SD as a threshold. Similarly, risk ratios and confidence intervals from sensitivity analyses on low risk of bias, fracture as an efficacy outcome and baseline denominators showed no statistically significant differences from the main analysis.

Figure 3.32: Alendronate 10 mg/day versus placebo, wrist fractures (sensitivity)



3.3.9 HEALTH-RELATED QUALITY OF LIFE

A meta-analysis was not conducted because only one study reported analyzable data for quality of life (97). The ROSE trial was a multicenter, open-label, one year trial examining alendronate 70 mg/week and zoledronic acid 5 mg/year with a primary focus on markers of bone turnover. Quality of

life was evaluated using the Qualeffo-41 questionnaire. The questionnaire had a range from 41 to 205 points which can be converted to a score from 1 to 100, where a lower score indicates higher quality of life. Although both zoledronic acid and alendronate both showed improvements in total score from baseline (zoledronic acid mean -1.2, SD 8.8 [n=394]; alendronate mean -0.6, SD 9.0 [n=186]), the changes were not statistically different between the two treatment groups.

3.3.10 WITHDRAWAL DUE TO ADVERSE EVENTS

Women who received alendronate 10 mg/day had a statistically non-significant 2% lower risk of withdrawing from a study due to adverse events compared to those who received placebo (95% CI: 0.76, 1.28), while those who received 5 mg/day had a non-significant 30% higher risk compared to placebo (95% CI: 0.94, 1.81). Eight studies provided data for the 10 mg dose (total 5716 participants), five for the 5 mg dose (total 2684 participants). Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.35.

Figure 3.33: Alendronate 10 mg versus placebo, withdrawal due to adverse events

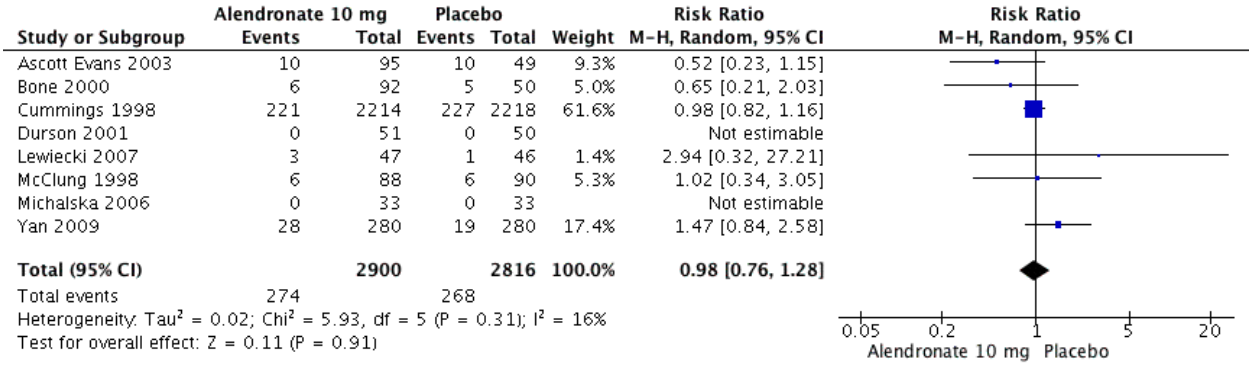


Figure 3.34: Alendronate 5 mg versus placebo, withdrawal due to adverse events

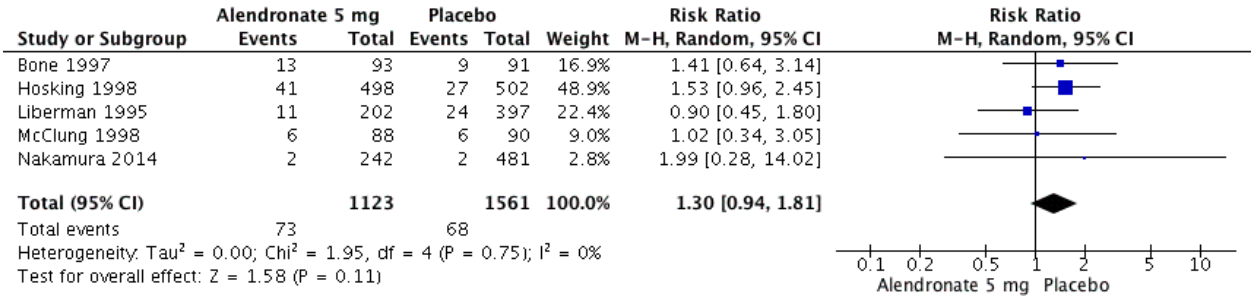
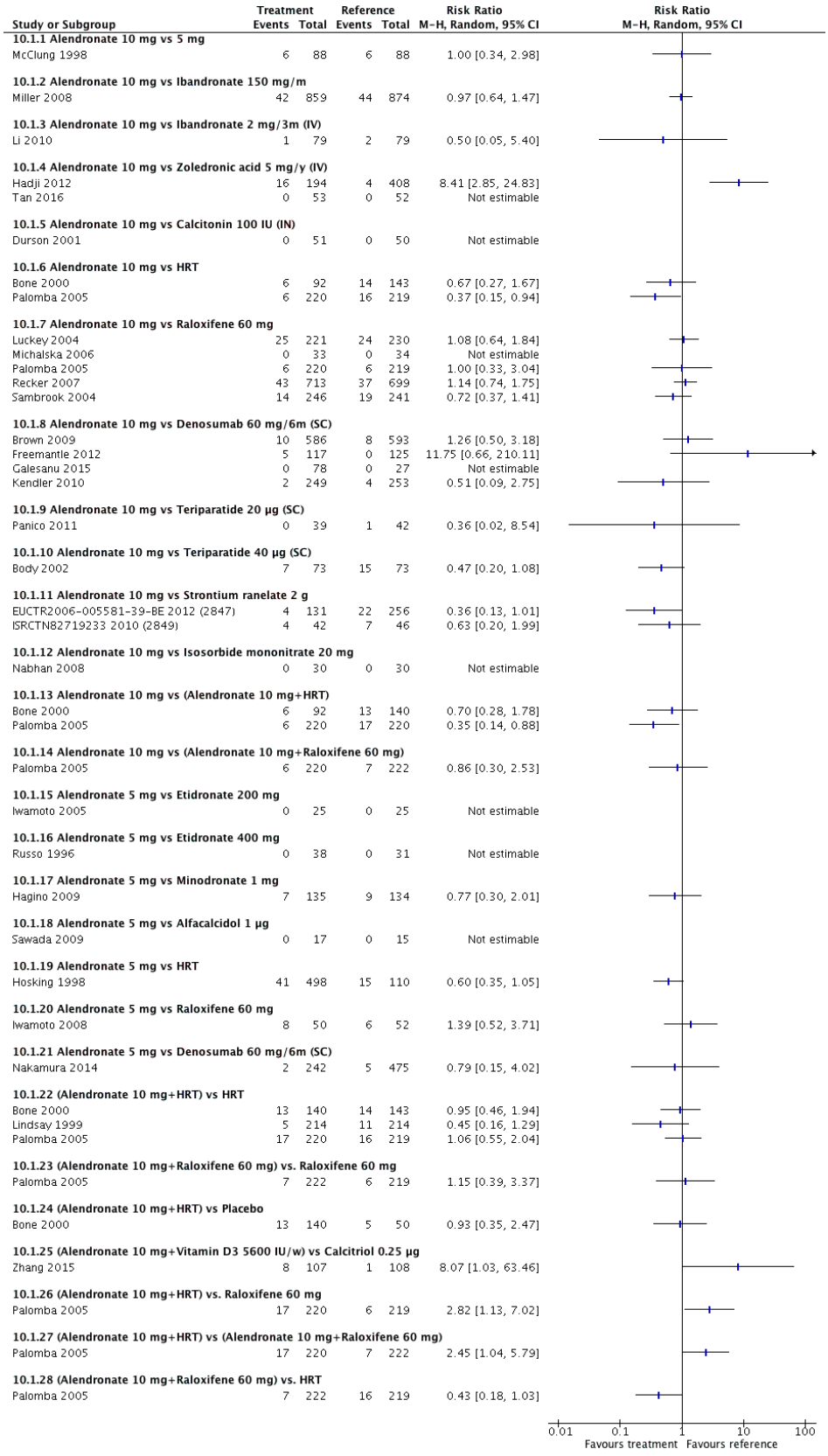


Figure 3.35: Alendronate versus active comparators or placebo, withdrawal due to adverse events



3.3.11 SERIOUS ADVERSE EVENTS

Women who received alendronate 10 mg/day had a statistically non-significant 1% increased risk of having a serious adverse event compared to those who received placebo (95% CI: 0.80, 1.28), while those who received 5 mg/day had a non-significant 8% lower risk compared to placebo (95% CI: 0.73, 1.17). Five studies provided data for the 10 mg dose (total 2913 participants), and four provided data for the 5 mg dose (total 2500 participants). Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.38.

Figure 3.36: Alendronate 10 mg versus placebo, serious adverse events

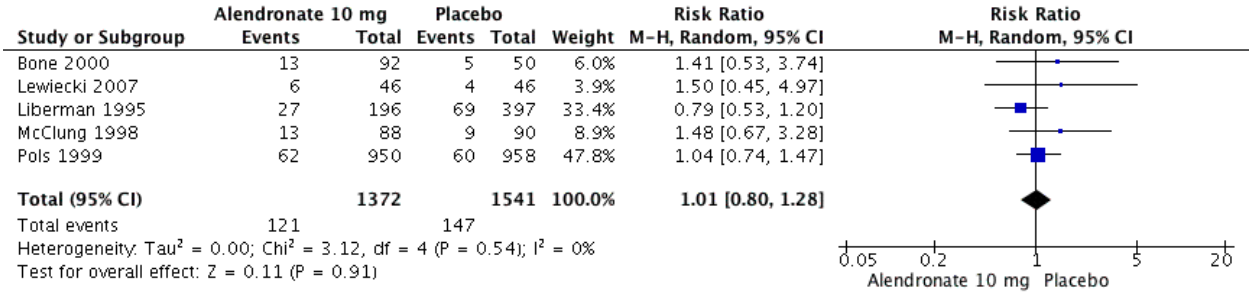


Figure 3.37: Alendronate 5 mg versus placebo, serious adverse events

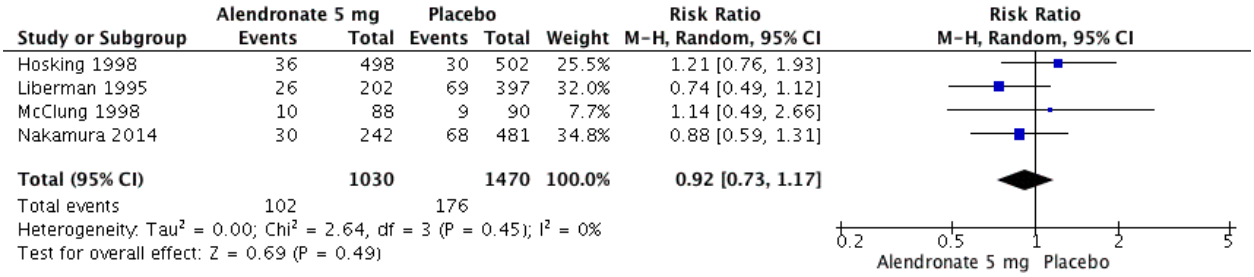
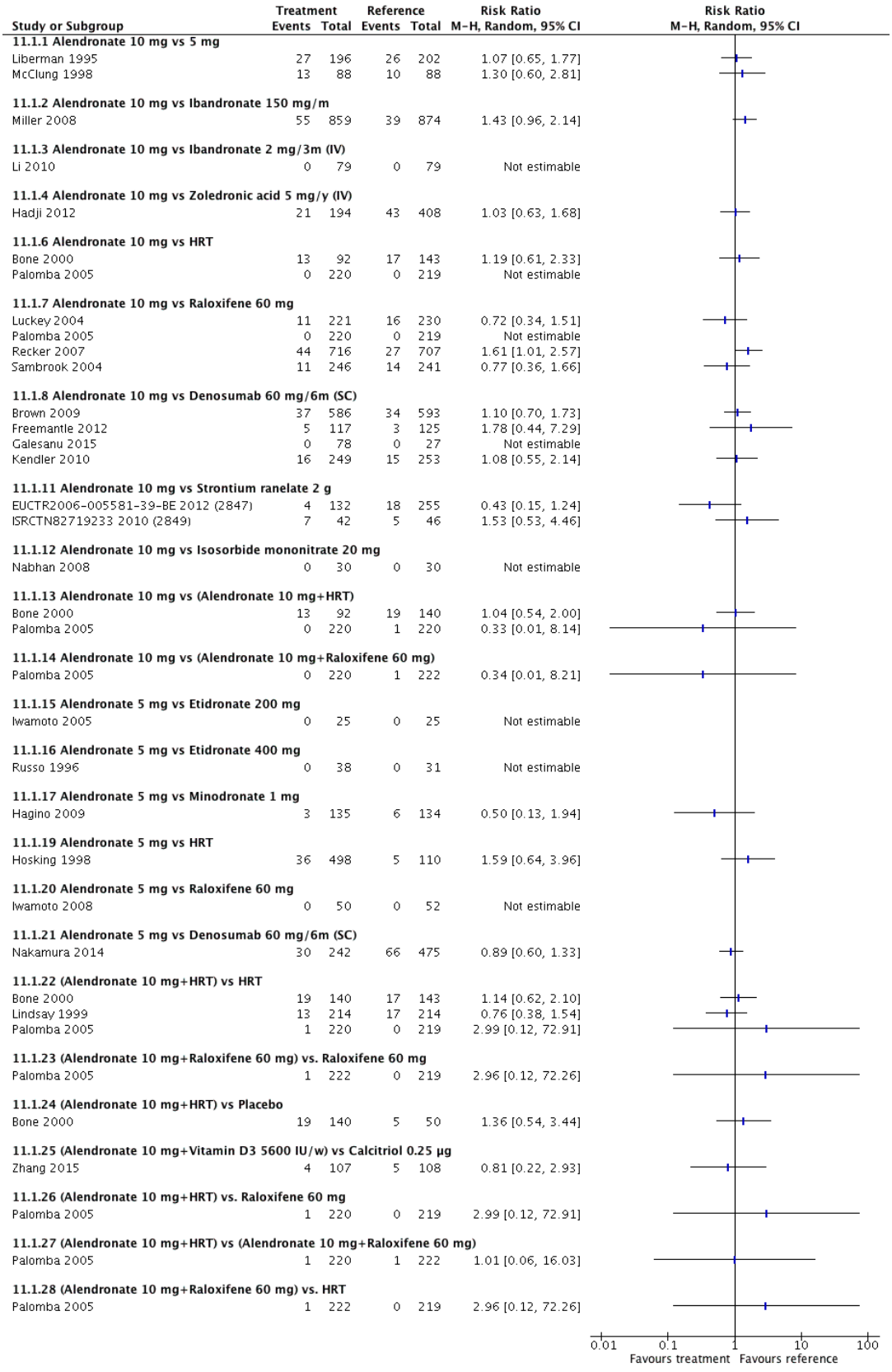


Figure 3.38: Alendronate versus active comparators or placebo, serious adverse events



3.3.12 GASTROINTESTINAL ADVERSE EVENTS

Women who received alendronate 10 mg/day had a non-significant 3% increased risk of gastrointestinal adverse events compared to those who received placebo (95% CI: 0.98, 1.08), while those who received 5 mg/day had a non-significant 3% lower risk (95% CI: 0.83, 1.13). Eleven studies provided data for the 10 mg dose (total 10497 participants), and three for the 5 mg dose (total 1777 participants). Additional comparisons are presented in Figure 3.41. Six of eleven studies for the 10 mg dose and one of two studies for the 5 mg dose excluded participants at baseline with some form of gastrointestinal disease. For example, trials specified in the exclusion criteria that those with “major upper gastrointestinal disease” (82) or “dyspepsia requiring daily treatment” (85) were not eligible for participation.

Figure 3.39: Alendronate 10 mg versus placebo, gastrointestinal adverse events

Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ascott Evans 2003	15	95	6	49	0.3%	1.29 [0.53, 3.11]
Black 1996	422	1022	402	1005	21.0%	1.03 [0.93, 1.15]
Bone 2000	25	92	11	50	0.6%	1.24 [0.66, 2.30]
Cummings 1998	1052	2214	1047	2218	60.4%	1.01 [0.95, 1.07]
Greenspan 1998	28	60	26	60	1.5%	1.08 [0.72, 1.60]
Greenspan 2002	54	163	57	164	2.5%	0.95 [0.70, 1.29]
Liberman 1995	64	196	114	397	3.6%	1.14 [0.88, 1.47]
McClung 1998	26	88	26	90	1.1%	1.02 [0.65, 1.62]
Michalska 2006	2	33	1	33	0.0%	2.00 [0.19, 21.00]
Pols 1999	202	950	185	958	7.3%	1.10 [0.92, 1.32]
Yan 2009	47	280	43	280	1.6%	1.09 [0.75, 1.60]
Total (95% CI)		**5193**		**5304**	**100.0%**	**1.03 [0.98, 1.08]**
Total events	1937		1918			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.95$, df = 10 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 1.07 (P = 0.29)

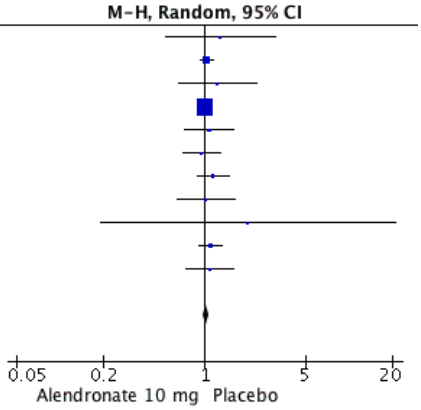


Figure 3.40: Alendronate 5 mg versus placebo, gastrointestinal adverse events

Study or Subgroup	Alendronate 5 m g Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hosking 1998	148	498	148	502	61.3%	1.01 [0.83, 1.22]
Liberman 1995	53	202	114	397	28.9%	0.91 [0.69, 1.21]
McClung 1998	23	88	26	90	9.8%	0.90 [0.56, 1.46]
Total (95% CI)		**788**		**989**	**100.0%**	**0.97 [0.83, 1.13]**
Total events	224		288			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 2 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 0.41 (P = 0.68)

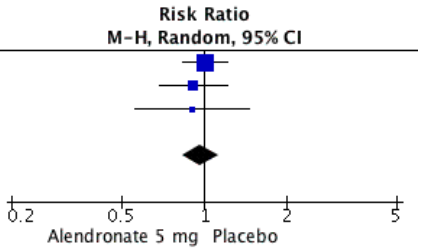
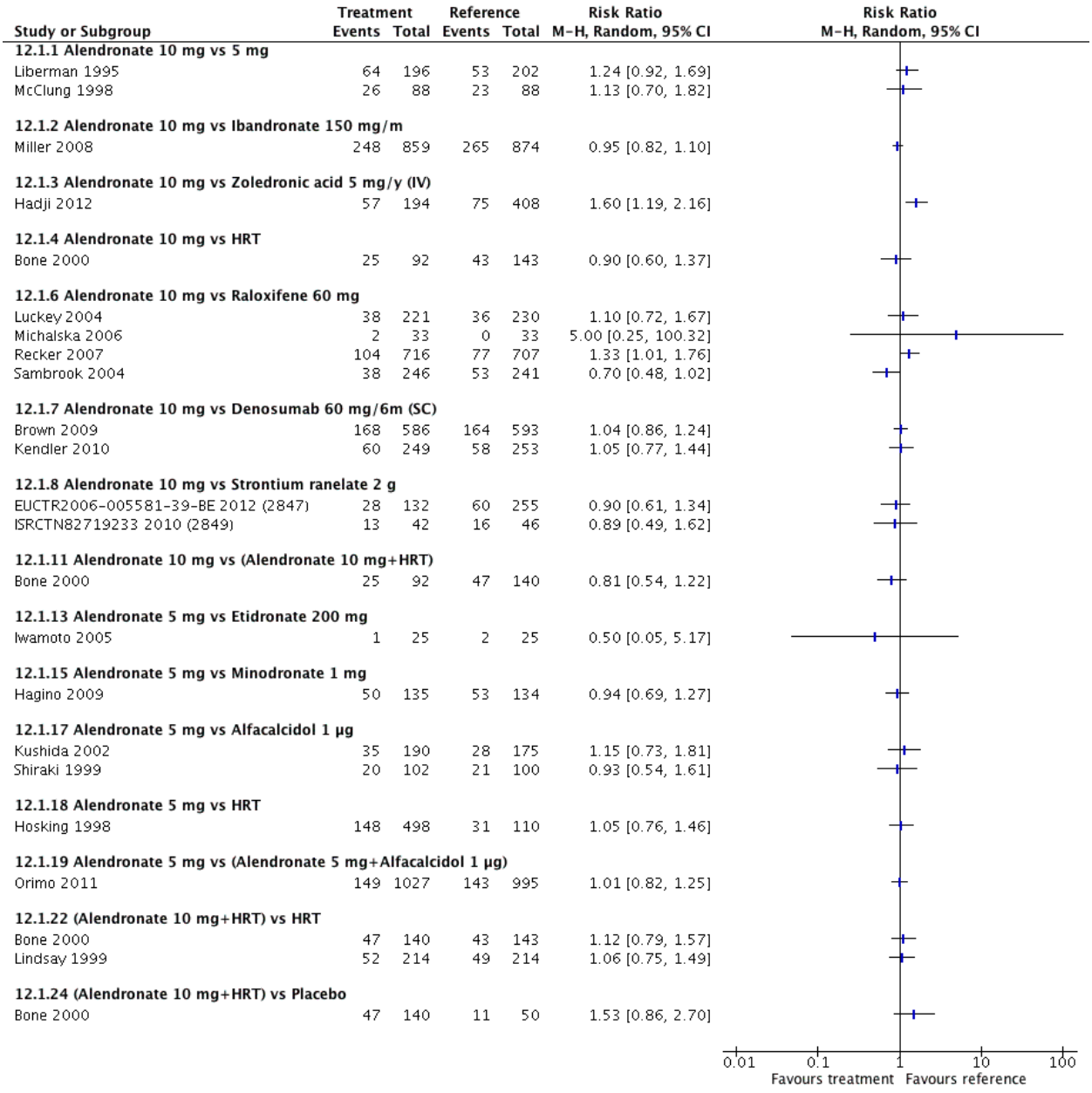


Figure 3.41: Alendronate versus active comparators or placebo, gastrointestinal adverse events



3.3.13 OSTEONECROSIS OF THE JAW

A meta-analysis could not be conducted because osteonecrosis of the jaw was reported by two studies with zero events. The FLEX study reported no events among 662 participants in the alendronate 10 mg/day arm and 437 participants in the placebo arm (87) while another study reported zero events among 242 participants in the alendronate 5 mg/day arm and 481 participants

in the placebo arm (84). Among active comparators, 4 studies provided data for osteonecrosis of the jaw indicating zero events (Figure 3.42).

Figure 3.42: Alendronate versus active comparators, osteonecrosis of the jaw

Study or Subgroup	Treatment Events	Total	Reference Events	Total	Risk Ratio M-H, Random, 95% CI
13.1.1 Alendronate 10 mg vs Ibandronate 2 mg/3m (IV)					
Li 2010	0	79	0	79	Not estimable
13.1.4 Alendronate 10 mg vs Zoledronic acid 5 mg/y (IV)					
Chavez-Valencia 2014	0	52	0	52	Not estimable
13.1.7 Alendronate 10 mg vs Denosumab 60 mg/6m (SC)					
Freemantle 2012	0	117	0	125	Not estimable
13.1.17 Alendronate 5 mg vs Denosumab 60 mg/6m (SC)					
Nakamura 2014	0	242	0	475	Not estimable

3.3.14 ATYPICAL FEMORAL FRACTURE

A meta-analysis was not conducted for atypical femoral fracture due to rarity of the adverse event. It was reported in five studies among the alendronate 10 mg/day trials and one study among the 5 mg/day dose trials (84). Additional comparisons beyond alendronate alone versus placebo are presented in Figure 3.45, where no event of atypical femoral fracture was found amongst these studies.

Figure 3.43: Alendronate 10 mg versus placebo, atypical femoral fracture

Study or Subgroup	Alendronate 10 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ascott Evans 2003	0	95	0	49		Not estimable
Bone 2000	0	92	0	50		Not estimable
Lewiecki 2007	0	46	0	46		Not estimable
Qin 2007	0	280	0	280		Not estimable
Yan 2009	0	25	0	22		Not estimable

Figure 3.44: Alendronate 5 mg versus placebo, atypical femoral fracture

Study or Subgroup	Alendronate 5 mg Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Nakamura 2014	0	242	0	481		Not estimable

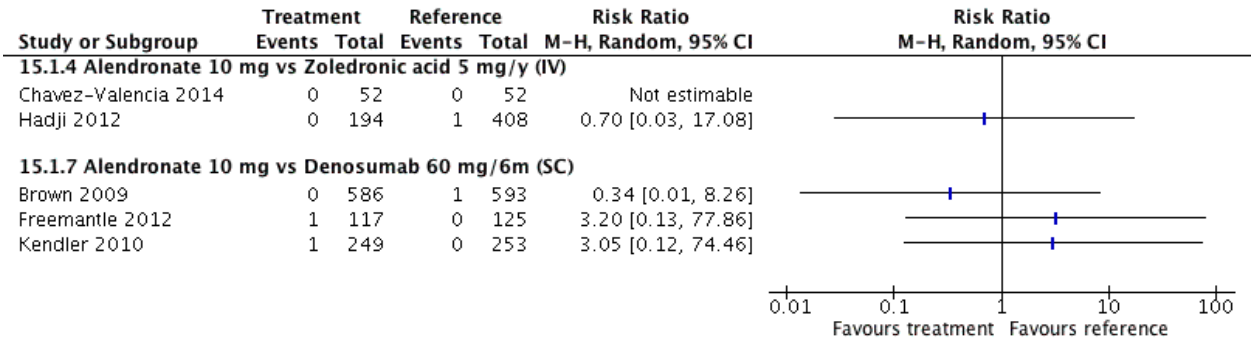
Figure 3.45: Alendronate versus active comparators, atypical femoral fracture

Study or Subgroup	Treatment Events	Total	Reference Events	Total	Risk Ratio M-H, Random, 95% CI
14.1.1 Alendronate 10 mg vs Risedronate 5 mg					
Akyol 2006	0	60	0	52	Not estimable
Galesanu 2011	0	132	0	32	Not estimable
Sarioglu 2006	0	25	0	25	Not estimable
14.1.2 Alendronate 10 mg vs Ibandronate 150 mg/m					
Galesanu 2011	0	132	0	33	Not estimable
14.1.4 Alendronate 10 mg vs Zoledronic acid 5 mg/y (IV)					
Chavez-Valencia 2014	0	52	0	52	Not estimable
Tan 2016	0	53	0	52	Not estimable
14.1.5 Alendronate 10 mg vs HRT					
Bone 2000	0	92	0	143	Not estimable
Eviö 2004	0	30	0	30	Not estimable
Palomba 2005	0	220	0	219	Not estimable
14.1.6 Alendronate 10 mg vs Raloxifene 60 mg					
Luckey 2004	0	221	0	230	Not estimable
Palomba 2005	0	220	0	219	Not estimable
14.1.7 Alendronate 10 mg vs Denosumab 60 mg/6m (SC)					
Freemantle 2012	0	117	0	125	Not estimable
Galesanu 2015	0	78	0	27	Not estimable
Kendler 2010	0	249	0	253	Not estimable
14.1.8 Alendronate 10 mg vs Teriparatide 40 µg (SC)					
Body 2002	0	73	0	73	Not estimable
14.1.9 Alendronate 10 mg vs Isosorbide mononitrate 20 mg					
Nabhan 2008	0	30	0	30	Not estimable
14.1.10 Alendronate 10 mg vs (Alendronate 10 mg+Vitamin K1 10 mg)					
Jokar 2016	0	23	0	24	Not estimable
14.1.12 Alendronate 10 mg vs (Alendronate 10 mg+HRT)					
Bone 2000	0	92	0	140	Not estimable
Eviö 2004	0	30	0	30	Not estimable
Palomba 2005	0	220	0	220	Not estimable
14.1.13 Alendronate 10 mg vs (Alendronate 10 mg+Raloxifene 60 mg)					
Palomba 2005	0	220	0	222	Not estimable
14.1.15 Alendronate 5 mg vs Etidronate 400 mg					
Russo 1996	0	38	0	31	Not estimable
14.1.16 Alendronate 5 mg vs Minodronate 1 mg					
Hagino 2009	0	135	0	134	Not estimable
14.1.17 Alendronate 5 mg vs Denosumab 60 mg/6m (SC)					
Nakamura 2014	0	242	0	475	Not estimable
14.1.18 (Alendronate 10 mg+HRT) vs HRT					
Bone 2000	0	140	0	143	Not estimable
Eviö 2004	0	30	0	30	Not estimable
Lindsay 1999	0	214	0	214	Not estimable
Palomba 2002	0	50	0	50	Not estimable
Palomba 2005	0	220	0	219	Not estimable
14.1.19 (Alendronate 10 mg+Raloxifene 60 mg) vs. Raloxifene 60 mg					
Palomba 2005	0	222	0	219	Not estimable
14.1.20 (Alendronate 10 mg+Teriparatide 20 µg (SC)) vs Teriparatide 20 µg (SC)					
Muschitz 2014	0	41	0	42	Not estimable
14.1.21 (Alendronate 5 mg+HRT) vs HRT					
Palomba 2002	0	50	0	50	Not estimable
14.1.22 (Alendronate 10 mg+HRT) vs Placebo					
Bone 2000	0	140	0	50	Not estimable
14.1.23 (Alendronate 10 mg+HRT) vs. Raloxifene 60 mg					
Palomba 2005	0	220	0	219	Not estimable
14.1.24 (Alendronate 10 mg+HRT) vs (Alendronate 10 mg+Raloxifene 60 mg)					
Palomba 2005	0	220	0	222	Not estimable
14.1.25 (Alendronate 10 mg+HRT) vs (Alendronate 5 mg+HRT)					
Palomba 2002	0	50	0	50	Not estimable
14.1.27 (Alendronate 10 mg+Raloxifene 60 mg) vs. HRT					
Palomba 2005	0	222	0	219	Not estimable
14.1.28 (Alendronate 10 mg+Teriparatide 20 µg (SC)) vs (Raloxifene 60 mg+Teriparatide 20 µg (SC))					
Muschitz 2014	0	41	0	34	Not estimable

3.3.15 ATRIAL FIBRILLATION

A meta-analysis was not conducted for atrial fibrillation because no cases were reported among alendronate doses compared to placebo. Five studies of alendronate 10 mg/day versus active comparators (zoledronic acid or denosumab) showed a total of four cases of atrial fibrillation but results were not pooled amongst comparators.

Figure 3.46: Alendronate versus active comparators, atrial fibrillation



3.3.16 PUBLICATION BIAS

Funnel plots assessing publication bias were made for two outcomes where alendronate 10 mg/day was compared to placebo that had at least ten studies (non-vertebral fractures, 10 studies; gastrointestinal adverse events, 12 studies). Standard error of the log risk ratio (vertical axis) is plotted against the risk ratio (horizontal axis) for each trial that reported the outcome of interest. The vertical dashed line indicates the pooled estimate. Studies with larger sample sizes and greater precision (*i.e.,* low standard error) are expected to be located on the upper area of the graph, while smaller studies are expected to be near the bottom of the graph. Asymmetry in the reversed funnel shape suggests publication bias. There may be asymmetry observed among studies reporting non-vertebral fracture since there is a gap in the lower right region of the graph where small studies favouring placebo are expected to be found. The pooled estimate may be dominated by larger trials favouring alendronate. There may also be asymmetry in the funnel plot for gastrointestinal adverse events, although the overall pooled effect is non-significant. Assessment of publication bias with

fewer than ten studies may not be reliable, thus funnel plots were not constructed for other outcomes (59).

Figure 3.47: Funnel plot of non-vertebral fractures

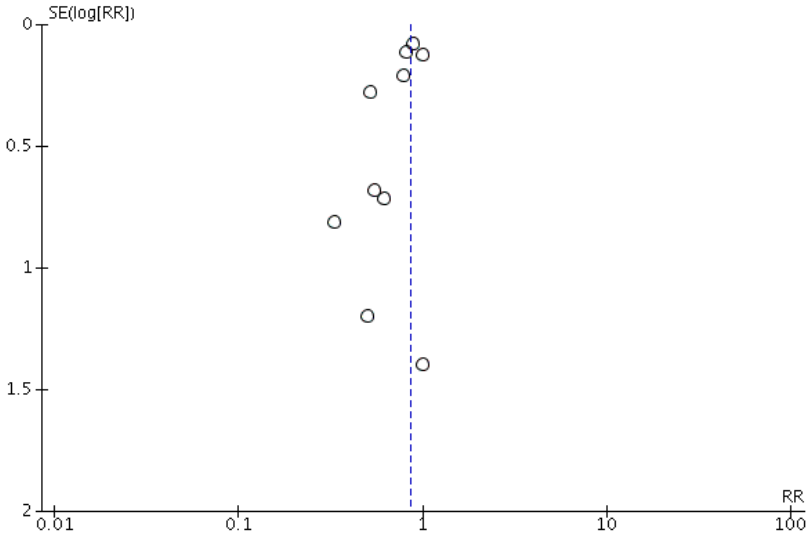
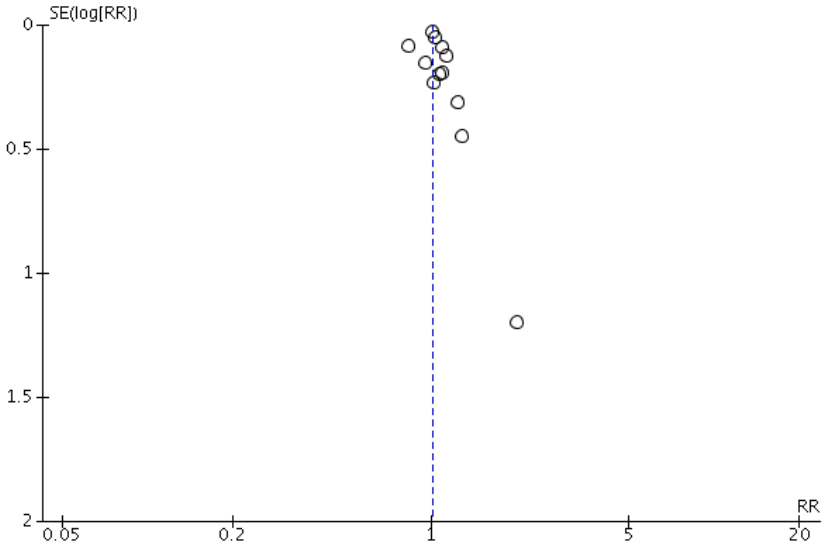


Figure 3.48: Funnel plot of gastrointestinal adverse events



3.3.17 SUMMARY OF FINDINGS TABLES

Summary of Findings tables were made for seven clinically important outcomes and both doses of alendronate: clinical vertebral fracture, hip fracture, wrist fracture, non-vertebral fracture, serious adverse events, and withdrawal due to adverse events. We evaluated the certainty of evidence using the GRADE approach for five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (74). In the table comparing alendronate 10 mg to placebo, high certainty of evidence was observed in radiographic vertebral fractures, non-vertebral fractures and hip fractures. We downgraded the evidence supporting clinical vertebral fracture, wrist fracuture, serious adverse events, and withdrawal due to adverse events by one level (indicating a serious limitation) for imprecision associated with few events and imprecise confidence intervals. We downgraded the evidence for wrist fracture by one level due to inconsistency caused by substantial heterogeneity in the main and subgroup analyses (*i.e.,* $I^2 \geq 50\%$). Potential factors that may be contributing to the observed heterogeneity are explored in the results for wrist fracture (Section 3.3.8.2). No serious limitations were detected in the domains for risk of bias, indirectness and publication bias.

Since few trials evaluated the 5 mg dose of alendronate, the quality of the evidence is limited by imprecision for most outcomes. Only radiographic vertebral fractures were judged to have high certainty of evidence for the 5 mg daily dose of alendronate. We downgraded clinical vertebral fracture, hip fracture and wrist fracture two levels (indicating very serious limitation) due to imprecision for including only one study with few events (*i.e.,* ≤ 2 events) in the analysis. The outcomes non-vertebral fracture, serious adverse events, and withdrawal due to adverse events were downgraded one level for imprecision due to few events, sample sizes and imprecise confidence intervals. Non-vertebral fracture was downgraded one level for inconsistency due to moderate heterogeneity in the main analysis (I^2=45%) and substantial heterogeneity in the subgroup analyses ($I^2 \geq 50\%$). Additionally, both adverse events outcomes were downgraded for high risk of performance bias due to lack of blinding or high risk of attrition bias due to substantial loss to followup. No serious limitations were detected in the indirectness and publication bias domains.

Table 3.5: Summary of Findings table (alendronate 10 mg/day or 70 mg/week versus placebo)

Patient or population: Postmenopausal women
Setting: Outpatients
Intervention: Oral alendronate 10 mg daily or 70 mg weekly
Comparison: Placebo (includes no treatment, placebo, background supplementation with vitamin D and/or calcium administered equally to all participants)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Alendronate 10 mg
Clinical vertebral fractures	3109 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.45** (0.28 to 0.73)	35 per 1,000	**19 fewer per 1,000** (25 fewer to 9 fewer)
Hip fractures	10793 (11 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.61** (0.40 to 0.93)	11 per 1,000	**4 fewer per 1,000** (7 fewer to 1 fewer)
Wrist fractures	9090 (9 RCTs)	⊕⊕◯◯ LOW [b,c]	**RR 0.82** (0.44 to 1.54)	28 per 1,000	**5 fewer per 1,000** (16 fewer to 15 more)
Non-vertebral fractures	10590 (11 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.83** (0.73 to 0.93)	104 per 1,000	**18 fewer per 1,000** (28 fewer to 7 fewer)
Serious adverse events	2913 (5 RCTs)	⊕⊕⊕◯ MODERATE [d]	**RR 1.01** (0.80 to 1.28)	95 per 1,000	**1 more per 1,000** (19 fewer to 27 more)
Withdrawal due to adverse events	5716 (8 RCTs)	⊕⊕⊕◯ MODERATE [e]	**RR 0.98** (0.76 to 1.28)	95 per 1,000	**2 fewer per 1,000** (23 fewer to 27 more)
Radiographic vertebral fractures	3513 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.55** (0.45 to 0.67)	74 per 1,000	**33 fewer per 1,000** (41 fewer to 24 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one level due to imprecision. There are few events (24 events) and the small sample size is unlikely to reach the optimal information threshold (3109 participants).
b. Downgraded one level due to high heterogeneity in the main analysis (I^2=60%), subgroup analysis for three years of treatment (I^2=50%), and sensitivity analyses including only studies with low risk of bias (I^2=80%), fracture as an efficacy outcome (I^2=86%) and baseline denominators (I^2=60%).
c. Downgraded one level for imprecision due to wide confidence interval crossing the null threshold and the 25% relative risk increase threshold suggested by GRADE.
d. Downgraded one level due to imprecision caused by the relatively low number of events (268 events) and relatively small sample sizes that are unlikely to reach meet the optimal information threshold (2913 participants).
e. Downgraded one level for imprecision due to wide confidence interval crossing the null threshold and the 25% relative risk increase threshold suggested by GRADE.

Table 3.6: Summary of Findings table (alendronate 5 mg/day or 35 mg/week versus placebo)

Patient or population: Postmenopausal women
Setting: Outpatients
Intervention: Oral alendronate 5 mg daily or 35 mg weekly
Comparison: Placebo (includes no treatment, placebo, background supplementation with vitamin D and/or calcium administered equally to all participants)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Alendronate 5 mg
Clinical vertebral fractures	1178 (2 RCTs)	⊕⊕◯◯ LOW [a]	not estimable	2 per 1,000	**2 fewer per 1,000** (2 fewer to 2 fewer)
Hip fractures	722 (1 RCT)	⊕⊕◯◯ LOW [b]	**RR 0.40** (0.02 to 8.21)	4 per 1,000	**3 fewer per 1,000** (4 fewer to 30 more)
Wrist fractures	178 (1 RCT)	⊕⊕◯◯ LOW [c]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Non-vertebral fractures	2084 (4 RCTs)	⊕⊕◯◯ LOW [d,e]	**RR 0.81** (0.45 to 1.46)	47 per 1,000	**9 fewer per 1,000** (26 fewer to 22 more)
Serious adverse events	2500 (4 RCTs)	⊕⊕◯◯ LOW [f,g]	**RR 0.92** (0.73 to 1.17)	120 per 1,000	**10 fewer per 1,000** (32 fewer to 20 more)
Withdrawal due to adverse events	2684 (5 RCTs)	⊕⊕◯◯ LOW [h,i]	**RR 1.30** (0.94 to 1.81)	44 per 1,000	**13 more per 1,000** (3 fewer to 35 more)
Radiographic vertebral fractures	1526 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.56** (0.35 to 0.90)	72 per 1,000	**32 fewer per 1,000** (47 fewer to 7 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded two levels for serious imprecision because only one study provided non-zero events for analysis (2 events).
b. Downgraded two levels due high imprecision from one study with 2 events, and wide confidence interval that crosses the null and thresholds for appreciable and harm (i.e., 25% relative risk reduction and 25% relative risk increase included in CI).
c. Downgraded two levels for imprecision due to one study with no events and small sample size (178 participants).
d. Downgraded one level for inconsistency due to moderate heterogeneity in the main analysis (I^2=45%), and high heterogeneity among subgroup analysis among bisphosphonate-naive participants (I^2=57%) and those with two years of treatment (I^2=62%). Within inconsistent meta-analyses, all individual study confidence intervals overlap; however, the treatment effect sizes suggested by the RR estimates differ.
e. Downgraded one level for imprecision related to the low number of events (40 events) and small sample sizes (2084 participants).
f. Downgraded one level for high risk of performance bias due to open-label design that may impact effect estimates for serious adverse events.
g. Downgraded one level for imprecision because of few events (278 events) and sample size (2500 participants).
h. Downgraded one level for high risk of performance bias in two studies (Hosking et al.,1998; Nakamura et al.,2014) with open-label design. One study (McClung et al.,1998) had a relatively low completion rate (~70%) that was slightly differential in various treatment groups (e.g., 64% and 72%) and may lead to attrition bias in the outcome.
i. Downgraded one level for imprecision due to few events (141 events) and relatively small sample sizes (2684 participants) unlikely to reach the optimal information size.

3.4 DISCUSSION

3.4.1 SUMMARY OF RESULTS

We included 58 studies in the meta-analyses examining ten outcomes. More studies were secondary prevention trials and compared the 10 mg daily alendronate dose to placebo. Both doses of alendronate were significantly better than placebo at reducing vertebral radiographic fractures. Only 10 mg/day was significantly better than placebo at reducing clinical vertebral, non-vertebral and hip fractures (Table 3.7, 3.8). No dose of alendronate was significantly better than placebo at reducing wrist fractures or improving quality of life. Both doses of alendronate were similar to placebo in terms of withdrawal due to adverse events, serious adverse events and gastrointestinal adverse events. No events were found for osteonecrosis of the jaw and atypical femoral fracture. Four cases of atrial fibrillation were found among alendronate compared to zoledronic acid or denosumab that showed no significant differences between the treatments for prevention of the event. Subgroup and sensitivity analyses included fewer studies, and results did not deviate significantly from the main analyses. Funnel plots showed possibility of publication bias for non-vertebral fractures. For the comparison of alendronate daily 10 mg to placebo, the Summary of Findings table indicates the quality of evidence was moderate to high in all outcomes except wrist fractures which was downgraded for imprecision and inconsistency. The overall certainty in evidence for the 5 mg daily dose of alendronate compared to placebo was low in all outcomes except for radiographic vertebral fracture, which had a high certainty of evidence. The most frequent reason for downgrading was imprecision (*i.e.,* low number of events, relatively small sample sizes, wide confidence intervals). Across both doses, high certainty of evidence was observed in the radiographic vertebral fractures. In the 10 mg dose, non-vertebral and hip fractures also had high certainty of evidence.

Table 3.7: Results of the systematic review for alendronate 10 mg/day versus placebo

Site of fracture	No. studies	RR (95% CI)		
		Overall	Primary prevention	Secondary prevention
Radio. vertebral	5	**0.55 (0.45, 0.67)**	**0.56 (0.39, 0.80)**	**0.55 (0.43, 0.69)**
Clinical vertebral	3	**0.45 (0.28, 0.73)**	0.34 (0.01, 8.26)	**0.46 (0.28, 0.73)**
Non-vertebral	9	**0.83 (0.73, 0.93)**	0.89 (0.76, 1.03)	**0.75 (0.63, 0.90)**
Hip	6	**0.61 (0.40, 0.93)**	0.79 (0.44, 1.44)	**0.48 (0.27, 0.86)**
Wrist	6	0.82 (0.44, 1.54)	1.20 (0.88, 1.64)	0.57 (0.30, 1.06)

*Bolded results are statistically significant.

Table 3.8: Results of the systematic review for alendronate 5 mg/day versus placebo

Site of fracture	No. studies	RR (95% CI)		
		Overall	Primary prevention	Secondary prevention
Radio. vertebral	4	**0.56 (0.35, 0.90)**	--	**0.56 (0.35, 0.90)**
Clinical vertebral	1	1.02 (0.06, 16.10)	1.02 (0.06, 16.10)	--
Non-vertebral	4	0.81 (0.45, 1.46)	1.22 (0.53, 2.80)	0.57 (0.32, 1.02)
Hip	1	0.40 (0.02, 8.21)	--	0.40 (0.02, 8.21)
Wrist	0	--	--	--

*Bolded results are statistically significant. Dashed lines indicate results were not estimable due to lack of study data.

3.4.2 COMPARISON TO LITERATURE

The current meta-analysis was intended as an update to the 2008 Cochrane review on alendronate and placebo (32). A comparison of the results from the current analysis (Tables 3.5, 3.6) to previous findings (Tables 3.7, 3.8) divided into overall, primary prevention, and secondary prevention populations showed identical trends in statistical significance. For example, the 10 mg dose is significantly better than placebo at risk reduction of vertebral, non-vertebral, and hip fractures in both main analyses. The main benefit of alendronate remains in secondary prevention trials. Both reviews found more studies comparing the 10 mg dose to placebo than the 5 mg dose, and no effect of daily 10 mg alendronate on wrist fracture prevention.

Table 3.9: Results of the Cochrane systematic review on alendronate 10 mg/day versus placebo

Site of fracture	No. studies	RR (95% CI)		
		Overall	Primary prevention	Secondary prevention
Vertebral	4	**0.55 (0.45, 0.67)**	**0.55 (0.38, 0.80)**	**0.55 (0.43, 0.69)**
Non-vertebral	5	**0.84 (0.74, 0.94)**	0.89 (0.76, 1.04)	**0.77 (0.64, 0.92)**
Hip	6	**0.61 (0.40, 0.92)**	0.79 (0.44, 1.44)	**0.47 (0.26, 0.85)**
Wrist	5	0.68 (0.34, 1.37)	1.19 (0.87, 1.62)	0.50 (0.34, 1.73)

*Bolded results are statistically significant.

Table 3.10: Results of the Cochrane systematic review on alendronate 5 mg/day versus placebo

Site of fracture	No. studies	RR (95% CI)		
		Overall	Primary prevention	Secondary prevention
Vertebral	3	**0.40 (0.29, 0.55)**	--	**0.40 (0.29, 0.55)**
Non-vertebral	2	0.95 (0.34, 2.67)	1.58 (0.82, 3.05)	0.55 (0.26, 1.18)
Hip	0	--	--	--
Wrist	0	--	--	--

*Bolded results are statistically significant.Dashed lines indicate results were not estimable due to lack of study data.

There are also several differences between the update and the original review. The update provides an estimate of the 5 mg dose for hip fracture prevention based on a secondary prevention study published in 2014 (84). Previously, the effect was not estimable. The original review did not divide vertebral fractures into radiographic and clinical types. Results of the update show there are fewer studies evaluating clinical vertebral fractures compared to radiographic vertebral fractures. While all alendronate doses are effective for preventing radiographic vertebral fractures, only the 10 mg dose of alendronate is more effective than placebo for preventing clinical vertebral fractures, and only among all or secondary studies. Only one primary prevention study was analyzable for clinical vertebral fracture prevention (82), and it did not show efficacy of alendronate for fracture prevention.

The original systematic review interpreted a risk reduction greater than 15% as a clinically significant difference. Carrying over this threshold to the current analysis, all comparisons that were statistically significant are also considered clinically significant. The lowest risk reduction that was also clinically significant was observed for non-vertebral fractures (17% reduction) in the comparison of alendronate 10 mg/day to placebo, while the greatest risk reduction that is also clinically significant was observed in clinical vertebral fractures (55% reduction) for alendronate 10 mg/day compared to placebo.

3.4.3 STRENGTHS AND LIMITATIONS

The results of this meta-analysis are believed to be robust as the review was conducted according to the accepted methodology for systematic reviews. The literature search performed by an experienced information specialist was comprehensive and covered multiple databases using a

variety of controlled vocabulary. Grey literature databases and regulatory agency reports were combed through for additional information, which may reduce the risk of publication bias and provide a more accurate effect estimate. Subgroup analyses were conducted to elucidate potential heterogeneity and variations in effect among subsets of the population, such as among those with severe osteoporosis versus osteopenia, previously treated versus not treated with bisphosphonates, and those receiving varying years of treatment. Sensitivity analyses were undertaken to determine the robustness of findings in relation to assumptions made during the meta-analysis, such as the threshold of 2 SD for classifying primary versus secondary prevention studies, including studies with any risk of bias, fractures reported in any form, and the participants in analysis as denominators. An additional advantage of this analysis is the separation of doses of alendronate which allows a distinction between the prevention (5 mg) and treatment (10 mg) doses when examining efficacy.

Limitations of this analysis include few number of studies found that examined combination treatments, durations longer than 3 years and studies comparing the 5 mg dose. These diminished the power of the analysis to detect significant differences between combination treatments, long-term bisphosphonate therapy and the 5 mg dose of alendronate. The low number of rare adverse events observed did not allow for meaningful analysis. A follow-up review including observational studies is likely to yield more events and will be comprehensive given that randomized, controlled trials have already been covered in the current analysis. An additional limitation regarding the outcome of gastrointestinal adverse events is the exclusion of participants with gastrointestinal disease. Of the 13 studies that provided data for incidence of gastrointestinal adverse events, seven trials excluded participants with major gastrointestinal illnesses. Although the directions of individual study effects were consistent regardless of medical history in the current analysis, in the future it may be beneficial to distinguish between trials that excluded or allowed participants with major gastrointestinal disease when examining gastrointestinal adverse events.

A methodological limitation that may have increased the estimates risk of are studies that lacked specifications regarding randomization and allocation concealment methods. Although these trials

may describe that randomization was done, it is not possible to mark them as low risk of bias because the method of randomization or allocation concealment was not available. We also used a cutoff of one year treatment duration with follow-up for including trials. While the threshold aimed to set a manageable scope that allowed focus on fracture trials, the limitation is loss of data from trials with less than one year duration that may report short-term safety outcomes. It is possible that these adverse events will be captured in long-term studies that include short-term effects, however it is nonetheless a loss of potentially important data. Another potential source of heterogeneity is the lack of uniform definitions for non-vertebral fractures. In order to gather a representative evidence base for non-vertebral fracture incidence, we included fracture data that reported any type of non-vertebral fracture as defined by the study authors. While this captured all types of non-vertebral fractures found within the literature search, it also led to greater variability in the data included as "non-vertebral fracture". Some studies may have used a definition of any fracture other than the spine, while others may have utilized a definition excluding fractures in the digits or the ankle because they could be caused by physical trauma rather than low bone mineral density (98). However, these studies would be extracted and analyzed together under non-vertebral fractures. This variability may have contributed to increased heterogeneity in the effect estimates, as observed by moderate to high I^2 values in non-vertebral fracture meta-analyses. The issue has been explored in literature. A study by MacKey et al. (2011) assessed the impact of varying definitions of non-vertebral fracture on treatment effects based on data from five trials (99). They re-analyzed non-vertebral fracture efficacy according to different definitions of the outcome (*e.g.,* any non-vertebral fracture, low-trauma non-vertebral fractures only, any non-vertebral fracture excluding the face and extremities). They found the summary hazard ratios were similar regardless of fracture definitions, ranging from 0.73 to 0.78 with overlapping confidence intervals. The authors recommended the use of "any non-vertebral fracture" as the optimal definition to reduce overall sample size due to a higher likihood of events and to provide the most complete estimate of treatment benefits for patients. However, the authors pooled data from one trial each of alendronate, clodronate, zoledronic acid, denosumab, and lasofoxifene, therefore further research is likely required with greater numbers of studies for each

treatment to improve generalisability. An additional source of heterogeneity is the lack of a standard method of reporting fractures. Fractures not assessed as efficacy outcomes were typically reported as safety adverse events. However, adverse event reporting is not uniform, and these included reporting fractures as total number of events without distinction between treatment groups, or generally as having occurred during the trial without specifying the numbers or site of fracture. It is unclear in some studies that reported no fracture events occurred whether a morphometric or radiographic assessment of vertebral fractures was conducted. This presents a source of heterogeneity that may be remedied in future studies by more rigorous reporting of fracture incidence whether in the main publication or in the trial registry.

3.4.4 CONCLUSION

We conducted a comprehensive systematic review and meta-analysis of the harms and benefits of alendronate alone and in combination for osteoporosis in postmenopausal women. The 10 mg dose of alendronate showed greater efficacy than placebo for reducing vertebral, non-vertebral and hip fractures, while the 5 mg dose showed efficacy in reducing radiographic vertebral fractures only. Alendronate was found to have a similar safety profile to placebo. A high certainty of evidence was found for radiographic vertebral fracture in both doses of alendronate, and non-vertebral and hip fracture in the 10 mg dose of alendronate. Results of the analysis mirrored previously conducted systematic reviews. More trials are needed to estimate the effect of 5 mg dose alendronate for prevention of wrist fractures.

CHAPTER 4: NETWORK META-ANALYSIS OF BISPHOSPHONATES

4.1 INTRODUCTION

Network meta-analysis (NMA), also known as mixed treatment comparisons, has evolved from traditional, pairwise meta-analysis to allow for multiple, simultaneous comparisons. In the absence of trials directly investigating the effects of two interventions of interest, results of NMA can provide indirect estimates of effect comparing the interventions (100). It is also advantageous to conduct a network meta-analysis where there is already direct evidence because additional indirect estimates from the model can contribute more precise and refined estimates of effect. 'Closed' loops are made when both direct and indirect evidence contribute to the same comparisons. In addition, a Bayesian framework allows the findings of an NMA to be interpreted as the estimation of a posterior probability of one intervention being superior to another which can facilitate the interpretation of findings (101).

There are three key assumptions underlying NMAs, of which the first two also pertain to traditional meta-analyses: similarity or exchangeability (between included trials), homogeneity (between pairwise comparisons), and consistency or transitivity (between direct and indirect evidence) (102). These assumptions are assessed based on the distribution of effect modifiers such patient age and disease severity among all included trials, studies in each pairwise comparison, and those involved in closed loops of evidence. Additionally, inconsistency can be evaluated by comparing the deviance from inconsistency and consistency models (103). These assumptions will be assessed in the following network meta-analysis.

4.2 METHODS

4.2.1 ELIGIBILITY CRITERIA

The inclusion criteria are summarized in Table 4.1. Randomized, controlled trials that enrolled postmenopausal women were included. Studies that enrolled both men and women but reported results separately by sex and trials that comprised of at least 95% postmenopausal women were also included to provide the maximum evidence base for answering the research question. However,

studies that included exclusively males, premenopausal women or those with secondary osteoporosis were excluded. Interventions of interest included seven bisphosphonates approved by regulatory agencies for the prevention or treatment of fractures in postmenopausal women, and three bisphosphonates that have been used off-label in populations of postmenopausal women for fracture prevention. Of the seven approved bisphosphonates, we only included studies that asssessed agency-approved doses to increase the generalisability of results and to better reflect available pharmacologic options in practice. In the analysis, we kept separate different doses of the same intervention (*e.g.,* alendronate 5 mg daily versus 10 mg daily) due to potential differences between their intended use (*i.e.,* prevention versus treatment). However, varying administration frequencies of the same total dose (*e.g.,* 5 mg daily versus 35 mg weekly) were combined to increase analysis power. In the absence of approved dosages, all doses of off-label bisphosphonates were included. Studies that compared the bisphosphonates, combinations of bisphosphonates, or combinations of bisphosphonates with non-bisphosphonate treatments were allowed. However, the network meta-analysis did not plan for an assessment of the individual efficacy of non-bisphosphonate treatments. The comparators were bisphosphonates or placebo, which included groups that received no intervention, matching placebo, or background supplementation with calcium and/or vitamin D at a dosage that is equally administered to all treatment arms.

Efficacy outcomes comprised of quality of life and the incidence of fractures (*i.e.,* number of women who sustained a fracture) divided into two vertebral and three non-vertebral types. Clinical or symptomatic vertebral fractures are more likely to occur in patients with more severe vertebral fractures (11, 13), hence it was separated from asymptomatic fractures identified radiographically or morphometrically. Safety outcomes were divided into two general outcomes (withdrawal due to adverse events, serious adverse events), two adverse events related to method of drug administration (gastrointestinal adverse events among oral bisphosphonates, acute phase response among intravenously administered bisphosphonates) and three rare adverse events (osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation). A variety of safety and efficacy outcomes were

selected to provide a well-rounded comparison between bisphosphonates. In line with the focus on fracture efficacy in the previously conducted Cochrane reviews, studies that assessed surrogate fracture endpoints such as bone mineral density changes, bone turnover markers, or bone microarchitecture that did not report at least one fracture outcome of interest were excluded at the data synthesis stage. We included studies of at least one year treatment duration. The threshold of one year was chosen to allow sufficient followup time to observe the effects of bisphosphonates on fractures in all sites, since non-vertebral fractures occur at a lower rate compared to other fractures (5). Additionally, the threshold is also clinically important, because the Canadian clinical practice guidelines recommend one year as the minimum amount of time before patients commencing bisphosphonate therapy should be re-assessed for fracture risk (7).

Reports and abstracts from all languages and countries were eligible. A study examining the impact of including grey literature in 135 meta-analyses of randomized controlled trials in various clinical areas found that on average, published works resulted in 15% larger estimates of intervention effect compared to the intervention effect including grey literature (63). This may be due to publication bias where studies with positive results are more likely to be published than trials showing null or negative results, thus leading to an exaggerated treatment effect (64). Although data from grey literature may be less rigorous due to lacking the peer-review stage mandatory for published data and the search methods may be less reproducible due to the lack of structure in searching grey literature databases, we decided to include grey literature to broaden the scope of evidence, to reduce the risk of publication bias and to potentially increase the validity of resulting effect estimates.

Table 4.1: Summary of selection criteria for network meta-analysis

	Inclusion criteria	Exclusion criteria
Population	Postmenopausal women	Premenopausal women, secondary osteoporosis, men (≥ 5% of participants)
Intervention	Bisphosphonates alone or in combination with other bisphosphonates or non-bisphosphonates. *Indicated for postmenopausal osteoporosis:* Alendronate, risedronate, etidronate, ibandronate, zoledronic acid, clodronate, minodronate. *Off-label use:* Tiludronate, neridronate, pamidronate	Non-bisphosphonate treatments alone (*e.g.,* estrogen, denosumab, raloxifene)
Comparator	Placebo (no treatment, or calcium and/or vitamin D) or other bisphosphonates	
Outcomes	*Efficacy* Vertebral fractures (radiographic) Vertebral fractures (clinical) Non-vertebral fractures Hip fractures Wrist fractures Health-related quality of life *Safety* Serious adverse events Withdrawal due to adverse events Gastrointestinal adverse events Acute phase response Osteonecrosis of the jaw Atypical femoral fracture Atrial fibrillation	Studies assessing surrogate endpoints (*e.g.,* bone mineral density, bone turnover markers, bone microarchitecture) that provide no fracture data are excluded from analysis
Study designs	Randomized controlled trials with ≥ 1 year treatment, conference abstracts	Non-randomized trials (*e.g.,* single arm extension, observational study), less than 1 year treatment
Other	No restrictions on language or country Both published and unpublished data (FDA, EMA, Health Canada drug approval reports, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform)	

4.2.2 SEARCH METHODS

The previous Cochrane reviews on alendronate, etidronate and risedronate conducted in 2008 compared the bisphosphonates to placebo, and did not include head-to-head comparisons of the bisphosphonates versus other active treatments (32-34). In order to address this issue and to gain greater insight on the availability of head-to-head trials in literature, a search update was conducted internally in 2012 that re-ran the original search strategy from the 2008 Cochrane reviews from

database inception to June 28, 2012. It intended to capture any excluded head-to-head trials of alendronate, risedronate or etidronate from previous reviews. In the process, the review authors screened all resulting abstracts from the search, re-assessing records that were included in the 2008 Cochrane reviews in addition to any new abstracts. Studies that met the PICOs criteria, which was identical to the 2008 Cochrane review with the exception of including head-to-head comparisons, were eligible for the analysis. In the current update, we built on the work conducted in the 2012 update for alendronate, etidronate and risedronate by assessing full-text records from the previous search. An experienced medical information specialist then updated the search strategies for the three interventions from June 28, 2012 to August 26, 2017 with a 6 month overlap (*i.e.,* from December 1, 2011) in order to ensure that all relevant articles within the expected timeframe are captured. For ibandronate and zoledronic acid, we based the current update on previous work conducted by members of the review team in 2011 for a graduate dissertation intended to be published as a Cochrane review (105), during which the literature searches were conducted from database inception to December 12, 2011. We also re-assessed full-texts included from the previous work. Thus, in the current update, the experienced medical information specialist updated the search strategies for ibandronate and zoledronic acid from December 12, 2011 to August 26, 2017 with a 6 month overlap (*i.e.,* from May 1, 2011). For the remaining off-label and unapproved bisphosphonates (*e.g.,* tiludronate, pamidronate, minodronate and clodronate), the search strategies were newly developed by the information specialist, peer-reviewed by another senior information specialist using the PRESS checklist (106), and were searched from database inception to August 26, 2017. All searches were conducted for the following databases on the Ovid platform: Embase Classic + Embase, Ovid MEDLINE® (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations), and the Cochrane Central Register of Controlled Trials. The search strategies used a combination of controlled vocabulary such as “Osteoporosis, Postmenopausal” and “Alendronate”, in addition to keywords such as “post-menopausal osteoporosis” and “bisphosphonates”. Vocabulary was adjusted across databases, and no restrictions were placed on language. The full search strategies appear in Appendix 2. A grey literature search of ClinicalTrials.gov and the WHO-ICTRP

Search Portal was performed on December 5, 2017 using the terms for each bisphosphonate. Studies retrieved from the clinical trial record databases were accessed at later dates for additional information. Drug approval reports and medical reviews developed by the United States Food and Drug Administration, the European public assessment reports by the European Medicines Agency, and the Drug Products Database by Health Canada were initially searched for extractable information on December 16, 2017.

4.2.3 STUDY RECORDS AND DATA MANAGEMENT

All retrieved records from the systematic literature search were stored a RIS file which entered a citation manager (Endnote X7, Clarivate Analytics) for de-duplication. Study records were first automatically de-duplicated in EndNote, and manually de-duplicated by both reviewers afterwards. Records were uploaded in bulk to a systematic review software (DistillerSR, Evidence Partners Inc.), where the screening of abstracts, full-texts, extraction of data and risk of assessments took place. Screening, data abstraction and risk of bias forms were created and piloted before study selection began. Extracted data were verified in DistillerSR and exported in the format of a Microsoft Excel file for analysis. Multiple reports of the same trial from published and unpublished sources were linked to prevent duplicate outcome extraction. At full-text screening, trial name, clinical trial registry identification, and references to previously published reports of the same trial were collected. This information was compiled to identify and group multiple published or unpublished records of the same trial. Outcomes included in each individual report were compared and assessed for data extraction, and the study with the most extractable outcomes is considered the principle study. Risk of bias assessments and all subsequent data extraction from other reports of the same trial were extracted on the principle study record. In the event of multiple reporting of the same outcome within the same trial, the most recent, adjudicated report of the outcome was extracted.

4.2.4 STUDY SELECTION

Study abstracts were screened in duplicate by two trained and independent reviewers for inclusion based on the eligibility criteria. Full-texts of potentially relevant abstracts were retrieved and uploaded into DistillerSR for the next round of screening. If there was uncertainty regarding eligibility of the study based on the abstract alone, the study would be included for full-text screening. Where it was likely the record was an abstract (*e.g.,* conference name clearly stated, single page, page numbers accompanied with letters), it was screened as a full-text based on the available information for inclusion. Any discrepancy marked by the software was discussed between reviewers until consensus was reached. If a consensus could not be reached, the issue was discussed with a third reviewer. Reviewers were not blinded regarding study authors or location.

4.2.5 DATA EXTRACTION

Information was extracted regarding the publication (*e.g.,* author, year of publication, trial name, clinical registry number, published protocol, linked companion studies), study design, (*e.g.,* primary study outcome, inclusion and exclusion criteria), and participant characteristics (*e.g.,* calcium and/or vitamin D supplementation, prior treatment experience, sample size, age, mean lumbar spine T-score, and participants with baseline vertebral fractures). For each intervention group, we recorded the dose, frequency, and route of administration. Outcome data included definitions of the outcomes provided by the study authors, duration of treatment, and analysis population (*e.g.,* intent-to-treat, modified intent-to-treat, per protocol, or safety). For dichotomous outcomes, we recorded the number of people with events, total randomized participants and total participants included in the analysis. For quality of life, we recorded the total number of randomized and analyzed participants, baseline values, end of trial measurements, and the change from baseline if available. Data for study characteristics, participants characteristics and outcomes were extracted by one reviewer using standardized abstraction forms in DistillerSR and subsequently verified by a second reviewer. Any discrepancy found by the second reviewer relating to the accuracy of data extracted by the first

reviewer was resolved through discussion with both reviewers, and if necessary, with a third reviewer. A study by Buscemi et al. (2006) compared the accuracy of data extracted by a single reviewer with verification by a second reviewer to double independent data abstraction by two reviewers a systematic review assessing melatonin for the management of sleep disorders (65). They found a statistically significant greater number of errors in single data extraction with verification (78 errors *vs* 51 errors; p=0.007). However, double independent extraction took 49.0 minutes longer per article which translated to a statistically significant increase from single data extraction with verification (p=0.003). The authors concluded that greater inaccuracy in single data extraction with verification did not translate to a substantial difference in the resulting effect estimates in terms of "direction, magnitude, precision or significance of pooled estimates for most outcomes". We used single data extraction with verification primarily to decrease the time cost. However, we also tried to set up measures to reduce inaccuracy and bias associated with single data extraction with verification. Both reviewers were extensively trained prior to data extraction, through collaboratively developing the data abstraction form, standardizing definitions for data extraction items, and researching literature in order to gain familiarity with the subject domain.

A vertebral fracture was considered radiographic if the study authors defined the fracture as "asymptomatic", "radiographic", "morphometric", or referenced a quantitative or semi-quantitative assessment. If the vertebral fracture was reported as "clinical", "symptomatic", or as an adverse event, it was classified as a clinical vertebral fracture. Non-vertebral, hip and wrist fractures were extracted as defined by the authors. In the case of unclear definitions, femoral neck fractures were inferred as hip fractures and distal radius or Colles' fractures were inferred as wrist fractures. The unit of measurement is the number of people with fractures. Health-related quality of life was extracted as a total score regardless of the outcome measure. Safety outcomes were recorded as defined by the study authors. Withdrawal due to adverse events was extracted as the number of participants who discontinued from the study.

4.2.6 RISK OF BIAS IN INDIVIDUAL STUDIES

Risk of bias was assessed by two reviewers using the Cochrane Collaboration's domain-based risk of bias tool for RCTs (59). Seven domains of bias representing five types of bias were assessed: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. In addition, two domains were assessed separately for subjective/objective outcomes and efficacy/safety events. Disagreements on risk of bias were resolved by discussion.

Blinding was evaluated separately for subjective and objective outcomes, since subjective outcomes in unblinded studies may be prone to greater risk of bias than objective outcomes (59, 66). Although objective outcomes may include a degree of subjectivity, they tend to be less person-based and places greater emphasis on standardized criteria or equipment output. Objective outcomes are all fractures, jaw osteonecrosis, atrial fibrillation, and atypical femoral fracture. Subjective outcomes are quality of life, withdrawals due to adverse events, acute phase response, serious and gastrointestinal adverse events. Evaluation of incomplete outcome data was separated for efficacy and safety outcomes since analysis populations may differ. In judging risk of attrition bias, we first examined the end-of-trial followup. If it included at least 80% of randomized participants, the study is likely at low risk of bias. The threshold of at least 80% of randomized participants completing followup was based on the system developed for the grading of evidence in *Evidence-Based Rheumatology* (67). Trials that lost more than 20% of randomized participants were considered to be at high risk of attrition bias which may lead to reduced study power and differential loss of participants where those that are remained in the trial are more or less likely to have the outcome of interest compared to those who left the trial (68). As a result, effect estimates from the analysis will be inaccurate and validity of the network meta-analysis will be impacted. However, attrition bias can occur even with greater than 80% followup rates if the withdrawal rates are significantly differential and participants are not missing at random (69). Therefore, in trials with greater than 80% followup,

we assessed attrition bias additionally by comparing withdrawal rates and the reasons for discontinuation across all treatment groups. If possible, we assessed whether the causes may be related to the outcome (*i.e.,* if the reason for withdrawal may be due to sustaining a fracture or adverse event, or if the reason is unlikely to be related to the outcome of interest). For studies that had less than 80% followup, we also assessed whether they used appropriate methods for dealing with missing data (*i.e.,* multiple imputation as opposed to last observation carried forward), and if the analysis population was representative of randomized participants (*i.e.,* intent-to-treat as opposed to per-protocol analysis). A combination of factors including a threshold for followup completion and comparisons of withdrawal rates across treatment groups were used to assess the likelihood of attrition bias due to incomplete outcome data for efficacy and safety outcomes.

4.2.7 DATA ANALYSIS

Studies eligible for analysis were assessed qualitatively for clinical heterogeneity to determine if the participants, intervention and outcome characteristics are sufficiently alike to allow meaningful interpretation of the pooled results. Bayesian network meta-analyses were conducted in the WinBUGS program (MRC Biostatistics Unit, Cambridge, UK) using a binomial likelihood model allowing adjustments for multi-arm trials. Vague priors were used for baseline values and basic parameters. Informative priors were used for binary outcomes to account for heterogeneity between RCTs (107). Placebo was selected as the reference treatment for all outcomes, which includes no treatment, placebo treatment or background supplementation with the same level of calcium or vitamin D as all other treatment groups. The effect estimates, 95% credible intervals, and standard deviations were derived using Markov Chain Monte Carlo simulations. The random-effects model was chosen for analyses because it assumes and adjusts for heterogeneity between trials, whereas the fixed-effects model assumes the between-trial heterogeneity to be zero (108). The goodness of fit was assessed using the deviance information criterion (DIC) and residual deviance, with lower DIC and residual deviance values indicating better fit. Three chains were included for each analysis

with at least 10000 iterations, and burn-in of at least 10000 iterations. Convergence was assessed visually for spikes and instability using the Gelman-Rubin plots, and for values close to 1.0 in the Gelman-Rubin statistic. The consistency assumption of the network was evaluated by plotting the mean posterior deviance from parameters of inconsistency models on the vertical axis with posterior deviance of consistency models (*i.e.,* models used in analysis) on the horizontal axis. Consistency is expected in the outcome when points follow a diagonal trend line with approximately equal x and y values. However, deviations toward the lower half of the trend line indicate inconsistency because the parameter has greater deviance under the analysis model than under the inconsistency model (*i.e.,* better fitting the inconsistency model). Results of the network meta-analyses are presented in league tables, also known as staircase diagrams (109). The treatment of interest for each comparison is indicated by the first cell of each row, and the reference treatment is represented by the first cell of each column highlighted in grey. Green cells (or light grey in a monochromatic manuscript) with black bolded font indicate a statistically significant preventive effect of the treatment of interest versus the reference treatment. For example, in row 3 and column 1 of Table 4.2, alendronate 10 mg/day is significantly more effective than placebo at reducing the odds of fracture or an adverse event. Red cells (or darker grey in a monochromatic manuscript) with white bolded font indicate a statistically significant increase in odds of a harmful event in the treatment of interest versus the reference treatment. For example, in row 4 and column 1 of Table 4.2, participants receiving risedronate 5 mg/day have greater odds of fracture or adverse events compared to those taking placebo. Although methods for ranking treatments are available, such as the surface under the cumulative ranking curve (SUCRA), the decision to present treatment rankings from NMAs is controversial. SUCRA generates a numerical value from 0 to 100% for each intervention in the NMA indicating the likelihood of being the best-ranked treatment (110). A higher value indicates a greater likelihood that the intervention is in the top ranks and the interpretation of rankings depends on whether the outcome is a harm or benefit. While it may be used to conveniently summarize the multitude of comparisons generated from network meta-analyses, the ranking of treatments using SUCRA does not show the magnitude of differences between effect estimates at different ranks.

Therefore, some suggest rankings may be misleading because they could over-exaggerate treatment differences even when they are provided as secondary results (110). A study by Trinquart et al. (2016) found that among 58 network meta-analyses, the SUCRA estimates from 94.8% of comparisons showed no evidence of a difference between the best-ranked and second best-ranked treatments as defined by an overlap in the 95% credible intervals (111). The authors also stated that guidelines recommend readers of NMAs to place a greater importance on relative treatment effects as opposed to ranking. For these reasons, we decided to present the findings as relative treatment effects in the form of league tables to provide a comprehensive view of the results.

Network diagrams were drawn in the Microsoft Excel add-in NodeXL to provide visual representations of the network composition. Each node represents a treatment of interest or placebo, and interconnecting lines represent the number of randomized, controlled trials included in each direct comparison. The size of each node is proportional to the number of participants in the treatment arm across all trials for the outcome. Among studies deemed similar enough to pool, outcomes involving only two interventions will be evaluated using traditional pairwise meta-analyses (Review Manager 5.3, The Cochrane Collaboration). Outcomes with insufficient numbers of studies for analysis or high heterogeneity will be summarized descriptively.

Table 4.2: Example interpretation of staircase diagram for binary outcomes

PBO	**PBO**			
ALED5	OR (95% CrI) Alendronate 5 mg/d compared to placebo	**ALED5**		
ALED10	**OR (95% CI) Alendronate 10 mg/d compared to placebo**	OR (95% CrI) Alendronate 10 mg/d compared to 5 mg/d	**ALED10**	
RISD5	**OR (95% CI) Risedronate 5 mg/d compared to placebo**	OR (95% CrI) Risedronate 5 mg/d compared to alendronate 5 mg/d	OR (95% CrI) Risedronate 5 mg/d compared to alendronate 10 mg/d	**RISD5**

Green cellswith bolded black font indicate significant preventive effect or lower odds of adverse event, red cells with white bolded font indicate significant harmful effect or higher odds of adverse event. OR=odds ratio, CrI=credible interval, PBO=placebo, ALED5=alendronate daily 5 mg/weekly 35 mg, ALED10=alendronate daily 10 mg/weekly 70 mg, RISD5=risedronate daily 5 mg/weekly 35 mg/monthly 150 mg.

4.2.8 SUBGROUP ANALYSES

Subgroup analyses were decided *a priori* based on characteristics in subsets of patients or studies that may have varying impacts on estimates of treatment effect. We conducted three subgroup analyses:

i) *Secondary versus primary prevention trials:* It was hypothesized that patients with established osteoporosis and greater disease severity (*e.g.,* bone mineral density at least two standard deviations below the reference value or with prevalent vertebral fractures) may vary in treatment response compared to patients with osteopenia. Hierarchical criteria were established in previous reviews (32-34) to distinguish between secondary prevention trials with more severe osteoporosis patients and primary prevention studies with osteopenia participants.

ii) *Prior bisphosphonate experience:* Bisphosphonates have long half-lives ranging up to ten years in adults depending on the rate of bone turnover and resorption (112). Effects of alendronate on bone density were observed up to seven years after treatment withdrawal (72). Potential residual effects may affect the therapy response of participants previously treated with bisphosphonates compared to those who are bisphosphonate-naïve. Thus, a subgroup analysis was conducted where studies enrolling exclusively participants with prior bisphosphonate experience were compared against trials comprising solely of participants who have not been previously treated with bisphosphonates. Prior bisphosphonate experiences of participants in a trial were determined based on specifications in the inclusion and exclusion criteria.

iii) *Treatment durations:* Although the base case taken for review analysis utilizes the longest time point, it was hypothesized that the duration of treatment with alendronate may affect the antifracture efficacy of alendronate therapy. Thus, subgroup analyses were conducted for one up to five years, depending on the availability of data.

Classification criteria for primary and secondary prevention trials

Trials were separated into primary and secondary fracture prevention trials, as defined in the Cochrane reviews based on a hierarchical classification (32-34). A study is classified as a secondary fracture prevention trial if the inclusion criteria restricted participants to postmenopausal women with bone density at least 2 SD or more below the peak bone mass or to women who had already experienced a vertebral fracture. If inclusion criteria were unclear, a study was classified as a primary prevention study if the baseline average T-score (and SD) was within 2 SD of the mean or if the prevalence of baseline vertebral fractures was less than 20%. In the case of unclear inclusion and baseline information, a trial was considered a secondary prevention study if the average age was above 62 years.

4.2.9 SENSITIVITY ANALYSES

Sensitivity analyses were performed on efficacy outcomes to test the robustness of findings in relation to assumptions made in the meta-analysis. We examined differences between effect estimates of the main analysis and five sensitivity analyses.

i) *Low risk of bias:* Studies with low risk of bias in the domain of incomplete data for efficacy outcomes were analyzed separately because these studies are expected to be of higher quality, having over 80% followup of all randomized participants at the end of trial time point.

ii) *Fracture as efficacy outcome:* Studies with fracture as an efficacy outcome were analyzed to assess whether there are differences in reporting quality between trials designed to examine fracture outcomes versus those that were not powered to assess fracture outcomes and only reported them as adverse events. Studies with fracture as efficacy outcomes are hypothesized to have higher quality reporting of related statistical methods and may describe in greater detail the assessment criteria and locations of fracture incidences. This may impact the resulting effect estimates from analysis.

iii) *Re-classification of primary and secondary prevention studies:* A threshold of two standard deviations below the reference value for bone mineral density and T-score was adopted from previous reviews to classify primary and secondary prevention studies. However, the WHO criteria for osteoporosis defined those with the disease as having BMD at least 2.5 SD below the reference mean, or a T-score lower than -2.5 (22). Thus, a sensitivity analysis using the threshold of 2.5 SD to classify primary and secondary prevention studies was performed to assess whether a shift in criteria would impact effect estimates from subgroup analyses.

iv) *Randomized versus analysis denominators:* A sensitivity analysis was planned for randomized versus analysis denominators because some end-of-study data were extracted based on a smaller population than all randomized participants (*e.g.,* those with radiographs available for assessment for vertebral fractures). The extent of its impact on the effect estimates was investigated.

v) *Major bisphosphonates:* Studies assessing the five most used bisphosphonates (alendronate, risedronate, etidronate, ibandronate, or zoledronic acid) were analyzed separately and compared with the main analysis to determine if inclusion of off-label and less used bisphosphonates significantly impacted the primary findings.

Table 4.3: Summary of subgroup and sensitivity analyses for network meta-analysis

Subgroup analysis			
i)	Primary versus secondary prevention studies		
ii)	Studies with bisphosphonate-naïve patients versus studies with bisphosphonate-experienced patients		
iii)	Treatment durations of 1 up to 5 years		
Sensitivity analysis		**Main analysis**	
i)	Studies with low risk of bias	i)	Studies with any level of bias
ii)	Studies with fracture efficacy outcome	ii)	Studies reporting fractures in any form
iii)	Primary prevention: BMD/T-score at most 2.5 SD below mean Secondary prevention: BMD/T-score at least 2.5 SD below mean	iii)	Primary prevention: BMD/T-score at most 2 SD below mean Secondary prevention: BMD/T-score at least 2 SD below mean
iv)	Denominator as number randomized	iv)	Denominator as number in analysis
v)	Studies including one of five major bisphosphonates	v)	Studies including one of ten bisphosphonates

4.3 RESULTS

4.3.1 CHARACTERISTICS OF STUDIES

The initial search yielded 5,856 records, and 2,849 abstracts were screened after de-duplication. Five hundred and eighty-eight full text records were assessed, including 266 full-texts originating from three previously published Cochrane reviews, an update conducted in 2012, and a dissertation conducted by members of the review team in 2011 (105) (grey box in PRISMA flow diagram, Figure 4.1). Four hundred and sixty-nine records were excluded. Examples of 'wrong study design' include single-arm extension studies and non-randomized designs, 'wrong study population' includes secondary osteoporosis and men with osteoporosis, 'wrong intervention/comparator' includes discontinuation of treatment studies or trials with unspecified treatment intervention arms (*e.g.,* standard care). Full-text records could not be obtained for three abstracts and are classified as 'awaiting full-text'. A detailed list of included full-text records from the network meta-analyses are shown in Appendix 5, and excluded full-text records are in Appendix 6.

No new studies were found in any of the grey literature databases or regulatory agency reports; however, three records from Clinicaltrials.gov and four medical reviews by the FDA (three on alendronate, one regarding ibandronate) provided extractable data. Information provided by grey literature allowed the inclusion of two studies previously excluded due to not reporting relevant outcome data. Of these two studies, one did not report fractures in the main publication but the Clinicaltrials.gov trial registry record reported fractures as adverse events (97). The second trial by Bone et al. (2000) reported fractures as "any clinical fracture adverse effect" without further specification in the main publication (95) but a FDA report specified the sites of incidence. Four FDA reports (77-79, 113) provided data for eight studies in addition to Bone et al. (2000). Of the eight studies, three publications were previously excluded due to not reporting fractures (114-116). Although fracture data was later found in FDA reports, they remained excluded from analysis because data from grey literature were not specified by fracture site. The remaining five studies were already included; however, FDA reports provided additional usable information. Four studies

obtained additional fracture or safety outcomes (81, 82, 117, 118) and one study obtained additional baseline participant information (119). No extractable data were found in various bisphosphonate reports in the Drug Products Database of Health Canada and among the European public assessment reports of the EMA. The bibliographies of reviews published after 2008, the publication year of the last Cochrane review, were searched but no additional studies were found.

A total of 97 unique RCTs and 22 companion records with usable data were included in the qualitative analysis. Of 97 trials, 47 studies were found from the most current literature search and 50 studies were found from previous searches. Forty-three RCTs originated from previously conducted Cochrane reviews and the internal 2012 update on alendronate, etidronate and risedronate. Five RCTs assessing ibandronate originated from previous dissertation work conducted by the review team, and two RCTs assessing zoledronic acid originated from the same dissertation (105). However, 15 studies were excluded from analysis: nine studies due to having one arm remaining once unapproved or unauthorized dosages were removed (*e.g.,* zoledronic acid 1 mg/year) (Table 4.5), and six studies due to having one arm after pooling regimens with the equivalent total dosage (*e.g.,* 5 mg daily and 35 mg weekly) (Table 4.6). The study and patient characteristics of these trials were not observed to be substantially different from those included in analysis.

Eight-three studies met the criteria for inclusion into network meta-analyses. However, only eighty-two records were included because a publication by Reginster et al. (120) contained two studies (Study Non Fx and Study Fx) with different inclusion and sample sizes which were counted as two individual trials in analysis (Table 4.4).Included studies were generally comparable in terms of potential effect modifiers such as mean age and disease severity (Table 4.4).

Sixty-eight trials enrolled women with established osteoporosis and were classified as secondary trials. Fifteen studies were classified as primary prevention trials. The treatment durations of studies ranged from 48 weeks to five years. The longest treatment durations were reported in two studies that provided four-year outcome data and two studies that provided five-year data. All participants were women at least 6 months postmenopausal except for three studies that included men (84, 121,

122). Mean lumbar spine T-scores varied from -3.4 to -1.3. The mean age of participants across trials ranged from 46.2 to 78.5 years. Fourteen trials included only those without vertebral fractures, and ten trials included only those with prevalent vertebral fractures at baseline. Thirty-six studies did not report information on how many participants had prevalent vertebral fractures at baseline. Trial sizes ranged from 40 participants to 9331 participants. Studies with smaller sample sizes were mostly not designed to test for fracture efficacy and fractures were reported as adverse events. Eighteen studies listed fracture incidence as the primary outcome and were larger trials with adequate power to examine relatively rare events.

All trials had parallel designs except for one study with a crossover design (123). The first year of the two-year crossover study examined clodronate administered 800 mg twice daily (1600 mg/day) for two weeks every three months compared to placebo. In the second year, the placebo group switched to 400 mg clodronate once daily, and the prior treatment group received placebo. Only the first period of the crossover was extracted. However, since the dosage of clodronate was higher than the approved dose for postmenopausal osteoporosis in Italy (800 mg/day), the study was excluded from analysis due to having only the placebo arm remaining after the removal of non-authorized doses.

Several studies modified the dose of treatment administered to participants during the study. Three studies increased the dose of alendronate from 5 mg/day to 10 mg/day, including both Fracture Intervention Trials where the dosage increased at two years of treatment in a three-year (86) or four-year trial (85), and a study where the dose was escalated after 18 months of a 30-month trial (88). Two studies reduced the dose of alendronate from 20 mg/day to placebo. One of these studies modified the dosage at one year of treatment in a two-year trial (89), and the other changed the dose at two years of a three-year trial (82). An additional study decreased the dose of alendronate from 20 mg/day to 5 mg/day after two years of treatment in a three-year trial (90). Dose modifications were justified due to the availability of newly published safety or efficacy results from other randomized, controlled trials. A two-year study assessing placebo, risedronate 2.5 mg/day, and risedronate 5

mg/day discontinued the 2.5 mg/day treatment arm at nine of thirteen centers before the end of trial due to the availability of new efficacy and safety data from other randomized, controlled trials (124). It was unclear when the discontinuation occurred. Outcomes were reported for the remaining participants after 76 women withdrew from the 2.5 mg/day arm.

Several extension studies were included in the analysis. The HORIZON study is a pivotal trial that examined the antifracture efficacy of zoledronic acid compared to placebo (125). Those who received zoledronic acid and completed the core three-year study were eligible for a three-year extension trial where participants were re-randomized to placebo or zoledronic acid (126). Participants who received zoledronic acid in the new randomization scheme were eligible for participation in a second extension trial where they were re-randomized to placebo or zoledronic acid for another three years (127). The Fracture Intervention Trials examining alendronate and placebo were also included (85, 86). Participants who received alendronate in any of two Fracture Intervention Trials (FIT) and completed treatment were eligible for the FLEX study, a five-year extension that examined the long-term efficacy of alendronate compared to discontinuing the bisphosphonate (87).

Table 4.4: Included studies in network meta-analyses

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Adami 2008	-	1 year	Secondary	Age 55 to 80 yrs, postmenopausal ≥ 5 yrs, BMD at least 2.5 SD below mean value in young adults, no lumbar vertebral fractures.	63.4 (7.1)	-	0%	Placebo NER 12.5 mg/2wk NER 25 mg/2wk NER 50 mg/2wk	IM	VID 800 IU CAL 1000 mg	188
Akyol 2006	-	1 year	Secondary	Postmenopausal ≥ 1 yr, OP diagnosis based on WHO criteria (T-score <-2.5).	56.7 (8.0)	-2.9 (0.6)	-	ALE 70 mg/wk RIS 35 mg/wk	Oral	CAL 1000 mg	112
Ascott-Evans 2003	-	1 year	Primary	Age < 80 yrs, postmenopausal ≥ 3 yrs, used HRT for ≥ 1 yr and discontinued within 3m of joining study, T-score between -1.5 and -3.5.	57.3 (6.6)	-2.3 (0.7)	0%	Placebo ALE 10 mg/d	Oral	CAL 500 mg	144
Bai 2013	-	2 years	Secondary	Postmenopausal, FN T-score <-2.5, or T-score <-1.5 with two or more vertebral fractures.	56.8 (6.6)	-	61%	Placebo ZOL 5 mg/yr	IV	VID 400 IU CAL 600 mg	483
Black 1996	FIT I (Vertebral Fractures)	3 years	Secondary	Age 55 to 81 yrs, postmenopausal ≥ 2 yrs, BMD more than 2 SD below PBM, at least 1 vertebral deformity.	70.8 (5.6)	-	100%	Placebo ALE 5-10 mg/d*	Oral	*CAL intake <1000 mg:* VID 250 IU CAL 500 mg	2027
Black 2007	HORIZON	3 years	Secondary	Age 65 to 89 yrs, T-score <-2.5, or vertebral fractures with T-score <-1.5.	73.1 (5.4)	-	63%	Placebo ZOL 5 mg/yr	IV	VID 400-1200 IU CAL 1000-1500 mg	7751
Black 2012	HORIZON (Extension 1)	3 years	Secondary	Women who received 3 ZOL or placebo infusions in the core HORIZON study.	75.5 (4.9)	-	61%	Placebo ZOL 5 mg/yr	IV	VID 400-1200 IU CAL 1000-1500 mg	1233
Black 2015	HORIZON (Extension 2)	3 years	Secondary	Women who had received at least the first and third doses of ZOL in E1 and completed the E1 study.	78.1 (4.8)	-	56%	Placebo ZOL 5 mg/yr	IV	VID 400-1200 IU CAL 1000-1500 mg	190
Black 2006	FLEX (FIT extension)	5 years	Secondary	In FIT, assigned to receive ALE, completed ≥ 3 yrs of treatment. Ineligible if TH T-score <-3.5 or lower than FIT baseline.	73.2 (5.7)	-1.3	34%	Placebo ALE 5 mg/d ALE 10 mg/d	Oral	VID 250 IU CAL 500 mg	1099
Bock 2012	-	1 year	Secondary	Age 60 to 75 yrs, postmenopausal > 5 yrs, total hip BMD T-score ≤−2.0 and >−3.5.	69.0 (3.0)	-	0%	Placebo IBA 150 mg/m	Oral	VID 400 IU CAL 500 mg	70
Bone 1997	Alendronate Elderly Osteoporosis Study	2 years	Secondary	Age 60 to 85 yrs, in good health apart from OP, LS BMD at least 2 SD below PBM.	70.7 (5.9)	-	37%	Placebo ALE 1 mg/d ALE 2.5 mg/d ALE 5 mg/d	Oral	CAL 500 mg	359
Bone 2000	-	2 years	Secondary	Age 42 to 82 yrs, postmenopausal, prior hysterectomy, LS BMD below 0.862 g/cm^2.	61.3 (8.0)	-2.5	-	Placebo ALE 10 mg/d CEE 0.625 mg/d Combination	Oral	VID ≤400 IU CAL 500 mg	425
Braga 2003	-	2 years	Secondary	Age < 80 yrs, postmenopausal ≥ 5 yrs, spine BMD at least -2.5 SD below PBM.	64.6 (7.7)	-3.4 (0.4)	-	Placebo NER 25 mg/m	Oral IV	VID 400 IU CAL 500 mg	78

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Cascella 2005	-	1 year	Secondary	Age 65 to 80 yrs, postmenopausal > 15 yrs, OP according to WHO criteria (BMD at least 2.5 SD lower than PBM).	72.7 (5.3)	-3.3 (0.2)	-	Placebo NER 25 mg/m	Oral	VID 400 IU CAL 500 mg	40
Chavez-Valencia 2014	-	1 year	Primary	Age 45 to 79 yrs, nonsurgical menopause, low BMD in the lumbar spine and/or right hip according to current diagnostic criteria.	58.3 (7.5)	-2.2 (0.8)	0%	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	VID 200 IU CAL 600 mg	104
Chesnut 1995	-	2 years	Secondary	Age 42 to 75 yrs, postmenopausal > 5 yrs, LS- BMD approximately 2 SD below PBM.	63.0 (6.3)	-	0%	Placebo ALE 5 mg/d ALE 10 mg/d ALE 20 mg/d* ALE 40 mg/d* ALE 2.5-40 mg/d*	Oral	CAL 500 mg	188
Chesnut 2004	BONE	3 years	Secondary	Age 55 to 80 yrs, postmenopausal ≥ 5 yrs, with 1-4 prevalent vertebral fractures (T4–L4) and BMD T-score of -2 to -5 in at least one vertebra (L1–L4).	69.0 (6.0)	-2.8 (3.6)	100%	Placebo IBA 2.5 mg/d IBA 20 mg/2d for 3m	Oral	VID 400 IU CAL 500 mg	2946
Cosman 2011	-	1 year	Secondary	Age 45 to 89 yrs, postmenopausal, FN, TH, or LS BMD T-scores <- 2.5, or T-score < -2 at any site and documented fracture.	65.0 (9.0)	-2.8 (0.3)	-	ZOL 5 mg/yr TER 20 µg/d Combination	IV SC IV+SC	VID 400-800 IU CAL 1000-2000 mg	412
Cummings 1998	FIT II (Clinical Fractures)	4 years	Primary	Age 55 to 80 yrs, postmenopausal ≥ 2 yrs, FN BMD <0.68g/cm^2 (around 2 SDs below PBM), no vertebral fracture.	67.7 (6.2)	-	0%	Placebo ALE 5-10 mg/d*	Oral	*If CAL<1000 mg, instructed to take:* VID 250 IU CAL 500 mg	4432
Delmas 2006	DIVA	2 years	Secondary	Age 55 to 80 yrs, postmenopausal ≥ 5 yrs, with LS BMD T-score< -2.5 but ≥ 5.	66.0 (6.2)	-3.3	-	IBA 3 mg/3 mos IBA 2 mg/2 mos IBA 2.5 mg/d	IV IV Oral	VID 400 IU CAL 500 mg	1382
Dursun 2001	-	1 year	Secondary	LS or FN-BMD at least 2 SDs or more below YAM.	61.2 (7.9)	-	-	Placebo CT 100 IU/d ALE 10 mg/d	Oral IN Oral	CAL 1000 mg	151
Eviö 2004	-	1 year	Secondary	Age 65 to 80 yrs, postmenopausal, with FN or LS BMD at least 2.5 SD below the PBM.	70.8	-	-	ALE 10 mg/d E2 2mg/d + NETA 1 mg/d Combination	Oral	VID 400 IU CAL 500-1000 mg	90
Fogelman 2000	-	2 years	Secondary	Age <80 yrs, postmenopausal ≥ 1 yr, mean LS T-score of <-2.	64.7 (7.2)	-2.9 (1.8)	29%	Placebo RIS 2.5 mg/d RIS 5 mg/d	Oral	CAL 1000 mg	543
Galesanu 2011	-	3 years	Secondary	Postmenopausal, OP diagnosis based on WHO criteria (BMD more than 2.5 SD below PBM).	63.3 (3.1)	-	-	ALE 79 mg/wk RIS 35 mg/wk IBA 150 mg/m	Oral	Not reported	198
Greenspan 1998	-	30 months	Secondary	Age > 65 yrs, entry criteria were not based on BMD.	71.1 (4.6)	-	-	Placebo ALE 5-10 mg/d*	Oral	*CAL <1000 mg:* VID 125 IU CAL 250 mg	122

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Greenspan 2002	-	2 years	Secondary	Age > 65 yrs, lives in local long-term care facilities, but not facilities that house independent, community-dwelling elderly persons, with LS or TH T-score <-2.0.	78.5	-	-	Placebo ALE 10 mg/d	Oral	VID 400 IU CAL 500 mg	327
Grey 2012	-	2 years	Primary	Postmenopausal ≥ 5 yrs, LS or TH BMD T-score between -1 and -2.5.	62.4 (8.5)	-1.3 (1.6)	0%	Placebo ZOL 1 mg/yr ZOL 2.5 mg/yr ZOL 5 mg/yr	IV	No supplementation	172
Hadji 2012	ROSE	1 year	Secondary	Age 55–90 yrs, postmenopausal, with TH or LS T-score ≤ −2.0 and clinical risk factors.	53.9 (8.0)	-2.7 (1.2)	-	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	VID 800 IU CAL 1200 mg	599
Hagino 2009	-	1 year	Secondary	Age ≥ 45 yrs, postmenopausal, with BMD below 70% YAM or (T-score < −2.6), or BMD below 80% YAM (T-score < −1.7) with one fragility fracture.	64.9 (6.8)	-3.1 (0.5)	33%	ALE 5 mg/d MIN 1 mg/d	Oral	CAL 200 mg	269
Harris 1999	VERT-NA	3 years	Secondary	Age < 85 yrs, postmenopausal ≥ 5 yrs, 2 or more vertebral fractures, or 1 vertebral fracture and LS T-score at least 2 SD below PBM.	68.7 (7.3)	-2.4 (4.3)	-	Placebo RIS 2.5 mg/d RIS 5 mg/d	Oral	CAL 1000 mg *If <40 nmol/L:* VID ≤ 500 IU	2458
Herd 1997	-	2 years	Primary	Postmenopausal ≥ 1 yr but ≤10 yrs, BMD at most 2 SD below averaged value for local, 50-year old women.	54.8 (5.0)	-	0%	Placebo ETI 400 mg/d (C)	Oral	CAL 500 mg	152
Hooper 2005	-	2 years	Primary	Postmenopausal 6 to 36 months, LS T-score > -2.5. Women with hysterectomy without bilateral oophorectomy are eligible if ages are between 51 to 60 yrs.	52.7 (3.2)	-0.4 (0.2)	18%	Placebo RIS 2.5 mg/d RIS 5 mg/d	Oral	CAL 1000 mg	383
Hosking 1998	-	2 years	Primary	Postmenopausal ≥ 6 months, in good health, with no clinical or laboratory evidence of systemic disease.	53.3 (4.0)	-	-	Placebo ALE 2.5 mg/d ALE 5 mg/d HRT*	Oral	No supplementation	1460
Ishida 2004	-	2 years	Secondary	Age < 75 yrs, postmenopausal ≥ 5 yrs, with OP diagnosis defined as either BMD 30% below YAM, or BMD 20% below YAM and one vertebral fracture.	46.2 (14.2)	-	31%	No treatment CEE 0.625 mg/d +MP 2.5 mg/d ETI 200 mg/d (C) CT 20 IU/wk ALF 1 µg/d VIK 45 mg/d	N/A Oral	No supplementation	396
Iwamoto 2005	-	1 year	Secondary	Age 55 to 86 yrs, postmenopausal, having OP defined as BMD < 70% of YAM or 70-80% of YAM with osteoporotic fractures.	70.7 (7.3)	-	-	ALE 5 mg/d ETI 200 mg/d	Oral	CAL 800 mg	50
Jokar 2016	-	1 year	Secondary	Postmenopausal, OP with T-score ≤-2.5.	-	-	-	ALE 70 mg/wk ALE 70 mg/wk +VIK 10 mg/d	Oral	VID 400 IU CAL 1000 mg	47

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Kasukawa 2014	-	1 year	Secondary	Age > 60 yrs, having OP defined as forearm BMD T-score <-2.5 SD for Japanese women, and no history of treatment for OP.	74.7 (6.3)	-	43%	RIS 17.5 mg/wk RIS 17.5 mg/wk +VIK 45 mg/d	Oral	Not reported	101
Lees 1996	-	2 years	Primary	Age 49 to 65 yrs, Caucasian, healthy, postmenopausal, no previous atraumatic or vertebral fractures.	57.7 (3.5)	-	0%	Placebo PAM 150 mg/d (C) PAM 300 mg/d (C)	Oral	No supplementation	121
Leung 2005	-	1 year	Secondary	Postmenopausal ≥ 5 yrs, LS BMD less than 2.5 SD of the local YAM.	67.0 (6.0)	-3.2 (0.3)	28%	Placebo RIS 5 mg/d	Oral	VID 400 IU CAL 500 mg	65
Lewiecki 2007	-	2 years	Secondary	Age < 80 yrs, LS-BMD T-score -1.8 to -4.0 or FN/TH T-score of -1.8 to -3.5 at the femoral neck or total hip.	62.5 (8.2)	-2.1 (0.8)	-	Placebo ALE 70 mg/wk DEN (7 arms)*	SC Oral SC	VID 400 IU CAL 1000 mg	412
Li 2005	-	1 year	Secondary	Age 45 and 68 yrs, postmenopausal ≥ 1 yr, in good health, LS T-score ≤-2.5.	-	-	-	Placebo RIS 5 mg/d	Oral	VID 125 IU CAL 600 mg	60
Liang 2017	-	2 years	Secondary	Age 50 to 65 yrs, newly diagnosed osteoporosis based on WHO criteria (T-score -2.5 to -3.3).	57.3 (3.0)	-	-	Placebo ZOL 5 mg/yr	IV	*1 tablet containing:* VID, CAL dose NR	285
Liberman 1995	Alendronate Phase III Osteoporosis Treatment Study	3 years	Secondary	Age 45 to 80 yrs, postmenopausal ≥ 5 yrs, with LS BMD at least 2.5 SD below PBM.	64.0	-	21%	Placebo ALE 5 mg/d ALE 10 mg/d ALE 20-5 mg/d*	Oral	CAL 500 mg	881
Lyritis 1997	-	4 years	Secondary	Age 67 to 77 yrs, postmenopausal, osteoporotic, with at least 1 vertebral collapse, low BMD below 2 SD, normal biochemical markers.	72.0 (0.4)	-	100%	No treatment ETI 400 mg/d (C)	Oral	VID: 2 µg) CAL 500 mg	100
Matsumoto 2009	-	2 years	Secondary	Age 55 to 80, with 1-5 vertebral fractures, LS BMD <80% (T-score <−1.7) of YAM.	71.5 (5.8)	-3.0 (2.0)	100%	Placebo MIN 1 mg/d	Oral	VID 200 IU CAL 600 mg	674
McCloskey 2004	-	3 years	Secondary	Postmenopausal or secondary OP, with spine T-score <2.5, and/or at least one prevalent vertebral fracture.	67.6 (7.8)	-	49%	Placebo CLO 800 mg/d	Oral	CAL 500 mg	483
McClung 1998	-	3 years	Primary	Age 40 to 59 yrs, healthy, postmenopausal 6 to 36 months.	41.5 (0.4)	-	0%	Placebo ALE 1 mg/d ALE 5 mg/d ALE 10 mg/d ALE 20 mg/d*	Oral	CAL 500 mg	447
McClung 2009	-	1 year	Primary	Aged 45 to 60 yrs, baseline mean LS BMD T-score between −1 and −2.5 and baseline T-score > −2.5.	53.5 (3.7)	-1.6 (0.3)	0%	Placebo IBA 150 mg/m	Oral	VID 400 IU CAL 500 mg	160

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
McClung 2001	HIP	3 years	Secondary	*Group 1:* Age 70 to 79 yrs with FN BMD T-score <- 4 SD, or FN T-score <-3 and ≥ 1 risk factor for hip fracture. *Group 2:* Age > 80 yrs with ≥ 1 risk factor for hip fracture, FN T-score <-4, or FN T-score <-3 and hip-axis length ≥ 11.1 cm.	77.7 (3.0)	-	30%	Placebo RIS 2.5 mg/d RIS 5 mg/d	Oral	CAL 1000 mg *If < 40 nmol/L:* VID ≤ 500 IU	9331
Meunier 1997	-	2 years	Primary	Caucasian, ambulatory, active, weighing 45 to 90 kg, within 15% of their normal BMI, postmenopausal 6 to 60 months, normal BMD (within 2 SD of the expected value for their age group).	52.7 (0.5)	-	-	Placebo ETI 400 mg/d (C)	Oral	CAL 500 mg	54
Michalska 2006	-	2 years	Secondary	Age 50 to 80 yrs, postmenopausal, with LS BMD T-score <-2.5, and previous treatment with alendronate (10 mg/d) ≥ 3 yrs, but did not participate in any clinical trials.	65.2 (6.7)	-	-	Placebo ALE 10 mg/d RAL 60 mg/d	Oral	VID 800 IU CAL 500 mg	99
Miller 2008	MOTION	1 year	Secondary	Age 55 to 84 yrs, postmenopausal ≥ 5 yrs, ambulatory, mean LS BMD T-score <–2.5 and ≥ –5.	65.6	-3.2	-	ALE 70 mg/wk IBA 150 mg/m	Oral	VID 400 IU CAL 500 mg	1733
Montessori 1997	-	3 years	Secondary	Age > 75 yrs old, ambulant, active, postmenopausal ≥ 1 yr, LS BMD 1 SD below age-matched controls (Z-score<-1 SD).	62.5 (6.2)	-	29%	Placebo ETI 400 mg/d (C)	Oral	CAL 500 mg	80
Mortensen 1998	-	2 years	Primary	Normal LS BMD (within 2 SD of age matched mean bone mass), postmenopausal 6 to 60 months, ambulatory, active, weigh between 45 kg to 90 kg, within 25% of their normal BMI.	51.5 (3.8)	-	0%	Placebo RIS 5 mg/d RIS 5 mg/d for 2 wks, placebo for 2 wks	Oral	No supplementation	111
Murphy 2001	-	18 months	Secondary	Postmenopausal ≥ 4 yrs, good health, FN BMD ≥ 2 SD below the PBM, ≤ 3 SD below age-specific mean.	72.1 (4.9)	-	-	Placebo ALE 10 mg/d MK-677 25 mg/d Combination	Oral	CAL 500 mg	292
Nakamura 2014	DIRECT	2 years	Secondary	Postmenopausal women and men, age >50 yrs, with 1-4 vertebral fractures, LS or TH BMD <80% Japanese YAM.	69.6 (7.5)	-2.7 (1.8)	98%	Placebo ALE 35 mg/wk DEN 60 mg/6m	SC Oral SC	VID 400 IU CAL 600 mg	1194
Nakamura 2017	-	18 months	Secondary	Treatment-naïve, postmenopausal Japanese women with primary OP.	73.0 (1.8)	-	17%	IBA 1 mg/m IBA 1 mg/m +ALF 1 µg/d	IV IV, Oral	Not reported	53
Orimo 2011	-	2 years	Secondary	Age >70 yrs, postmenopausal, with ≥ 1 risk factor for new fractures (*e.g.,* prevalent vertebral fractures, BMD < 3 SD of PBM, higher bone turn over marker levels).	76.6 (4.9)	-	56%	ALE 5 mg/d ALE 5 mg/d +ALF 1 µg/d	Oral	Not reported	2164

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Palomba 2002	-	2 years	Secondary	Hysterectomy with bilateral oophorectomy performed before natural menopause, LS BMD at least 2.5 SD below the mean bone density of the peak value for sex-matched healthy young adults (T-score < -2.5).	61.1 (3.8)	-	-	ALE 10 mg/d E2 2 mg/d Combination	Oral	VID 20 IU CAL tablet to achieve total daily dose >1000 mg	150
Palomba 2005	-	1 year	Secondary	Natural menopause, LS BMD at least 2.5 SD below the PBM of healthy young women (T-score < -2.5).	64.9 (4.1)	-3.2 (0.5)	-	ALE 10 mg/d CEE 0.625 mg/d +MP 2.5 mg/d RAL 60 mg/d ALE+RAL ALE+HRT	Oral	*CAL intake <1000 mg:* CAL 500 mg	1100
Pols 1999	FOSIT	1 year	Secondary	Age < 85 yrs, postmenopausal ≥ 3 yrs, LS BMD at least 2 SDs below mean of premenopausal women, in good health.	62.8 (7.4)	-	-	Placebo ALE 10 mg/d	Oral	CAL 500 mg	1908
Pouilles 1997	-	2 years	Primary	Caucasian, age 45 to 60 yrs, ambulatory, active, weigh between 45 and 80 kg, within 20% of the normal BMI, postmenopausal 6 to 60 months prior to enrolment, not been treated by HRT.	53.8 (3.1)	-	-	Placebo ETI 400 mg/d	Oral	CAL 500 mg	109
Reginster 2006	MOBILE	2 years	Secondary	Age 55 to 80 yrs, postmenopausal ≥ 5 yrs , mean LS BMD T score < -2.5 and -5.0.	66.0	-3.3	-	IBA 2.5 mg/d IBA 100 mg/m IBA 150 mg/m IBA 50+50 mg/m	Oral	VID 400 IU CAL 500 mg	1609
Reginster 2001	Study Non Fx	2 years	Secondary	Caucasian, Asian women, age 50 to 80 yrs, postmenopausal with LS BMD T-score <-2.	62.1 (6.6)	-	-	Placebo TIL 350 mg/m TIL 1400 mg/m	Oral	CAL 500 mg	488
Reginster 2001	Study Fx	3 years	Secondary	Caucasian, Asian women, age 50 to 80 yrs, postmenopausal with at least 2 mild or 1 moderate vertebral fracture but <5 vertebral fractures overall, and LS BMD T-score < -1.	67.4 (6.8)	-	83%	Placebo TIL 350 mg/m TIL 1400 mg/m	Oral	CAL 500 mg	1805
Reginster 2000	VERT-MN	5 years (2 years extension)	Secondary	Ambulatory women, age ≤ 85 yrs, postmenopausal ≥ 5 yrs, with at least two vertebral fractures.	71.0 (7.0)	-2.8 (1.1)	100%	Placebo RIS 2.5 mg/d RIS 5 mg/d	Oral	CAL 1000 mg *If <40 nmol/L:* VID ≤500 IU	1226
Robles-Carranza 2013	-	3 years	Primary	Postmenopausal women with low BMD and no other explanation for bone disease or previous fractures.	61.0 (9.6)	-	-	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	VID 400 IU CAL 1200 mg	118
Rossini 1999	-	2 years	Secondary	Age 58to 67 yrs, postmenopausal ≥ 5 yrs with BMD at least 2.5 SD below mean BMD of premenopausal healthy subjects.	61.3 (3.4)	-	-	No treatment CLO 100 mg/wk CLO 100 mg/2wk	N/A IM	*Diet adjusted:* CAL 1200-1300 mg	90

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Russo 1996	-	1 year	Secondary	Age 50 to 77 yrs, postmenopausal ≥ 1 yr, BMD lower than mean value in normal population -2.5 SD (Z-score) in 2 sites.	64.1 (6.2)	-	0%	ALE 5 mg/d ETI 400 mg/d (C) CLO 100 mg/wk-400 mg/d (C)	Oral Oral IM, Oral	Not reported	77
Sarioglu 2006	-	1 year	Secondary	Postmenopausal women with osteoporosis.	58.8 (6.9)	-	10%	ALE 70 mg/wk RIS 5 mg/d	Oral	VID 400 IU CAL 1000 mg	50
Shiota 2001	-	2 years	Secondary	Age > 50 yrs, postmenopausal, BMD < 0.70g/cm^2), visited the outpatient clinic of Saiseikai Yahata Hospital due to lumbo-dorsal pain.	61.7 (6.7)	-	-	Placebo ETI 200 mg/d (C)	Oral	ALF 0.5 µg CAL 2000 mg	40
Storm 1990	-	3 years	Secondary	At least 1 but no more than 4 atraumatic vertebral crush fractures.	68.4 (0.9)	-	100%	Placebo ETI 400 mg/d (C)	Oral	VID 400 IU CAL 500 mg	66
Tan 2016	-	3 year	Secondary	Diagnosed with postmenopausal osteoporosis at Huashan Hospital and Huadong Hospital based on WHO criteria (FN, LS, TH T-score ≤ -2.5).	68.0 (8.8)	-	-	ALE 70 mg/wk ZOL 5 mg/yr	Oral IV	Not reported	105
Tanakol 2007	-	3 years	Secondary	Age 47 to 74 yrs, postmenopausal ≥2 yrs, with LS or TH BMD at least 2.5 SDs below the mean for premenopausal women, or ≥1 non-traumatic vertebral fractures.	56.9 (8.0)	-	27%	Placebo CLO 800 mg/d	Oral	VID 400 IU CAL 500 mg	79
Välimäki 2007	-	2 years	Primary	Healthy, ambulatory, postmenopausal ≥ 5 yrs, LS BMD T-score between 2.5 and 1 SD below the PBM or ≥1 risks factor for osteoporosis.	65.9 (6.8)	-1.8 (0.4)	-	Placebo RIS 5 mg/d	Oral	VID 400 IU CAL 1000 mg	170
Watts 1990	-	2 years	Secondary	White and Asian women with osteoporosis, postmenopausal ≥1 yr, healthy, ≥1 but < 4 vertebral compression fractures.	65.1 (0.6)	-	100%	Placebo ETI 400 mg/d (C) PHO 2 g/d (C) Combination	Oral	CAL 500 mg	423
Wimalawansa 1998	-	4 years	Secondary	Postmenopausal Caucasian women with at least 1 but not more than 4 atraumatic vertebral fractures, and spine BMD at least 2 SD below PBM.	64.9 (0.9)	-	100%	No treatment ETI 400 mg/d (C) CEE 0.625 mg/d+ NG 150 mg/d (C) Combination	Oral	VID 400 IU CAL 1000 mg	72
Yan 2009	-	1 year	Secondary	Age ≤ 85 yrs, ambulatory postmenopausal ≥3 yrs, no prevalent vertebral fractures, LS BMD at least 2 SD below the mean bone mass of normal young Chinese women.	64.9 (6.2)	-	0%	Placebo ALE 70 mg/wk	Oral	*If levels are low:* VID 200 IU CAL 500 mg	560
Yang 2015	-	1 year	Secondary	Age 50 to 73 yrs, postmenopausal, recruited from community, LS or TH T-score ≤ −2.5 SD.	60.6 (9.2)	-	-	Placebo ZOL 5 mg/yr	IV	VID 400 IU CAL 1000 mg	100
Fukunaga 2002	-	48 weeks	Secondary	Age 40–75 yrs, ambulatory women or men, with involutional osteoporosis, LS BMD <70% of YAM without vertebral fracture, or <80% of YAM with vertebral fractures.	62.6 (6.2)	-3.0 (1.0)	14%	RIS 2.5 mg/d ETI 200 mg/d (C)	Oral	CAL 200 mg	235

Study	Trial name	Treatment duration	Prevention type	Summary inclusion/exclusion	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures (%)	Interventions, dose	Route of admin.	Supplements (units/day)	No. randomized
Qin 2007	-	1 year	Secondary	Age 50 to 75 yrs, postmenopausal, with fracture at distal radius in the past 5 yrs, and LS or hip T-score <-2.	59.8 (6.3)	-2.2 (0.8)	-	Placebo ALE 10 mg/d	Oral	CAL 1200 mg	47
Nakamura 2013	MOVER	3 years	Secondary	Age ≥ 60 yrs, ambulatory women or men, LS, TH, or FN BMD <80% of YAM and 1-5 vertebral fractures.	72.7 (6.3)	-2.7 (5.3)	100%	RIS 2.5 mg/d IBA 0.5 mg/m IBA 1 mg/m	Oral IV	VID 200 IU CAL 305 mg	1134
Pacifici 1988	-	2 years	Secondary	At least 1 nontraumatic vertebral fracture and/or evidence of spinal demineralization by quantitative computed tomography.	60.8 (8.2)	-	100%	Placebo ETI 400 mg/d (C) CEE 0.625mg/d+ MP 10mg/d (C)	Oral	CAL 1000 mg	93

Abbreviations: OP=osteoporosis, WHO=World Health Organization, BMD=bone mineral density, PBM=peak bone mass, YAM=young adult mean, SD=standard deviation, LS=lumbar spine, FN=femoral neck, TH=total hip. IM=intramuscular, IV=intravenous, IN=intranasal, SC=subcutaneous, C=cyclic regimen, m=months, yr=year, d=day, wk=week. ALE=alendronate, ETI=etidronate, RIS=risedronate, IBA=ibandronate, ZOL=zoledronic acid, CLO=clodronate, MIN=minodronate, PAM=pamidronate, TIL=tiludronate, DEN=denosumab, RAL=raloxifene, CT=calcitonin, HRT=hormone replacement therapy, CLC=calcitriol, CEE=conjugated equine estrogen, E2=estradiol, NETA=norethisterone acetate (progestin), MP=medroxyprogesterone (progestin), ISO=isosorbide mononitrate, ALF=alfacalcidol, VIK= vitamin K, MK-677=ibutamoren, PHO=phosphate, NG=norgestrel, VID=vitamin D, CAL=calcium, IU=international units.

*Study regimens and dose changes

Black 1996: Alendronate dose increased from 5 mg/d to 10 mg/d at the 24 month visit.
Chesnut 1995: Alendronate 20 and 40 mg/d doses changed to placebo at 12 months.
Cummings 1998: Alendronate dose increased from 5 mg/d to 10 mg/d at the 24 month visit.
Greenspan 1998: Alendronate dose was 5 mg/d until 18 months, and changed to 10 mg/d from 18-30 months.
Hosking 1998: For HRT, US centers administered CEE 0.625 mg/d+MP 5 mg/d while European centers gave a cyclic regimen of E2 2 mg/d+NETA 1 mg/d.
Lewiecki 2007: 7 denosumab arms: 6, 14, or 30 mg per 3m; 14 mg, 60, 100, or 210 mg per 6m.
Liberman 1995: Alendronate dose was 20 mg/d for 2 years followed by 5 mg/d for 1 year.
McClung 1998: Alendronate 20 mg/d for 2 years, placebo in third year.

Table 4.5: Studies excluded from analysis due to one arm after removing unauthorized doses (n=9)

Study	Trial name	Duration	Prevention type	Population characteristics	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures, (%)	Interventions dose	Route of admin.	Supplements (units/day)	No. randomized
Delmas 2008	-	2 years	Secondary	Age > 50 yrs, menopausal ≥ 5 yrs, BMD T-score (approximately) <-2.5, or BMD T-score <-2 and one vertebral fracture.	67.9 (8.2)	-3.1 (3.0)	33%	RIS 5 mg/d RIS 35 mg/wk RIS 50 mg/wk	Oral	CAL 1000 mg *If <30 nmol/L:* VID dose NR	1456
Frediani 2011	-	2 years	Secondary	Age 50 to 80 yrs, postmenopausal ≥ 5 yrs, LS BMD 2.5 SD below average value for 30-year-old women.	68.3 (8.0)	-3.0 (0.1)	38%	CLO 100 mg/wk CLO 200 mg/2wk	IM	*Study initiation:* VID 300 000 IU *Duration of study:* VID 800 IU CAL 1000 mg	60
Giannini 1993	-	1 year	Secondary	Age 42 to 79 yrs, BMD at least 2 SD below PBM.	51.1 (1.8)	-	86.1%	No therapy CLO 400 mg/d (C) CLO 400 mg/d +CLC 2 mcg/d (C)	N/A Oral Oral	*Asked to follow diet with:* CAL >800 mg	52
Giusti 2017	-	2 years	Secondary	Age 50 to 75 yrs, postmenopausal, LS-BMD T-score <-2.5 and no prevalent fractures.	65.8 (6.4)	-	0%	CLO 600 mg/m CLO 100 mg/wk	IV IM	Supplement dose not reported	72
Grey 2010	-	3 years	Primary	Postmenopausal ≥ 5 yrs, osteopenia (LS or TH BMD T-scores between -1 and -2).	63.5 (8.0)	-1.2 (0.3)	0%	Placebo ZOL 5 mg/3yr	IV	No supplementation	50
Li 2010	-	1 year	Secondary	Age 49 to 75 yrs, postmenopausal ≥ 1 yr, BMI 18-35 kg/m^2, LS or FN T-score <-2.0.	65.2 (7.3)	-	12%	ALE 70 mg/wk IBA 2 mg/3m	Oral IV	VID 200 IU CAL 500 mg	151
Recker 2004	-	3 years	Secondary	Age 55 to 76 yrs, postmenopausal ≥ 5 yrs, LS BMD T-score -2 to -5, 1-4 vertebral fractures.	66.9 (5.1)	-2.8	98%	Placebo IBA 0.5 mg/3m IBA 1 mg/3m	IV	VID 400 IU CAL 500 mg	2860
Reid 2002	-	1 year	Secondary	Postmenopausal, age 45 to 80 yrs, postmenopausal ≥5 yrs, with T-score <-2 and 1 vertebral fracture.	42.1 (6.5)	-	0%	Placebo ZOL 0.25 mg/3m ZOL 0.5 mg/3m ZOL 1 mg/3m ZOL 2 mg/6m ZOL 4 mg/yr	IV	VID ≤ 1000 IU CAL 1000 mg	351
Tsai 1999	-	1 year	Primary	Age 46 to 67 yrs, postmenopausal, with osteopenia (LS BMD values between −1 and −2.5 SD below the mean normal for premenopausal Chinese women).	56.3 (1.0)	-	6%	Placebo CLO 1600 mg/d for 2 wks per 3m (C)*	Oral	VID 65 IU CAL 300 mg	54

Abbreviations: OP=osteoporosis, BMD=bone mineral density, SD=standard deviation, LS=lumbar spine, FN=femoral neck, TH=total hip. IM=intramuscular, IV=intravenous, N/A=not applicable, C=cyclic regimen, m=months, yr=year, d=day, wk=week. ALE=alendronate, IBA=ibandronate, ZOL=zoledronic acid, CLO=clodronate, VID=vitamin D, CAL=calcium, IU=international units.

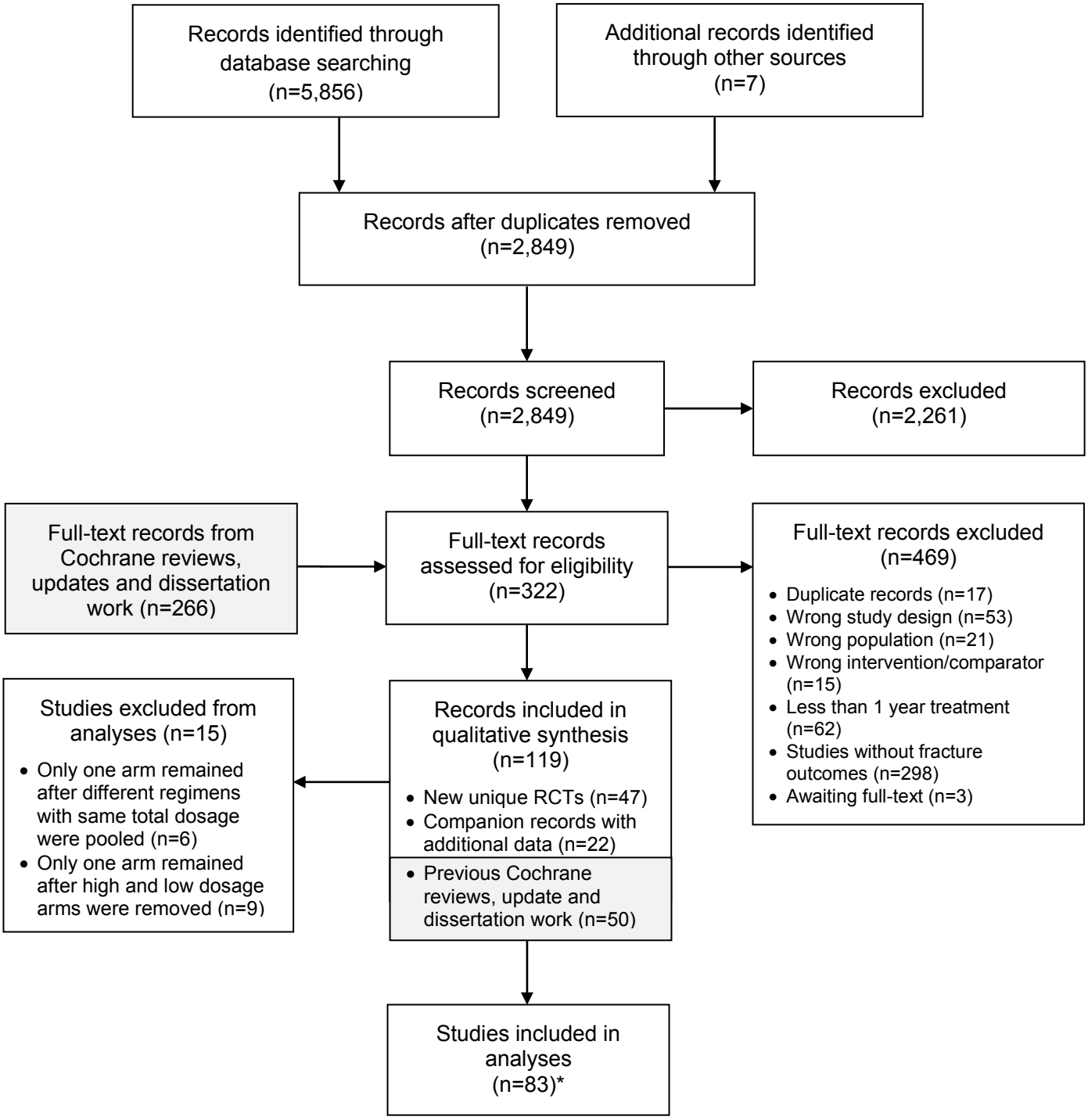
*Tsai et al., 1999: Crossover study where only the first year was extracted.

Table 4.6: Studies excluded from analysis due to one arm after pooling regimens with same total dose (n=6)

Study	Trial name	Duration	Prevention type	Population characteristics	Age (year), mean (SD)	LS T-score, mean (SD)	Prevalent vertebral fractures, (%)	Interventions dose	Route of admin.	Supplements (units/day)	No. randomized
Brown 2002	-	2 years	Secondary	Age > 50 yrs, postmenopausal ≥ 5 yrs, BMD T-score (approximately) <-2.5, or BMD T-score <-2 and one vertebral fracture.	67.9 (8.2)	-3.1 (3.0)	33%	RIS 5 mg/d RIS 35 mg/wk RIS 50 mg/wk	Oral	CAL 1000 mg *If <30 nmol/L:* VID dose NR	1456
Delmas 2008	-	2 years	Secondary	Age > 50 yrs, postmenopausal ≥ 5 yrs, LS BMD T-score <−2.5 or <−2.0 with at least one prevalent vertebral fracture.	64.9 (7.5)	-3.2 (0.6)	29%	RIS 5 mg/d RIS 150 mg/m	Oral	VID 400-1000 IU CAL 1000 mg	1292
Gu 2015	-	1 year	Secondary	Age 50 to 80 yrs, postmenopausal ≥1 yr, BMI 18 to 30, no severe lumbar anatomical abnormalities, osteopenia (-1 to -2.5 SD, age ≥ 65 yrs, or menopausal ≥ 10 yrs) or osteoporosis (FN, LS or TH T-score <-2.5, or <-1 and one fracture).	63.0 (6.8)	-	-	RIS 5 mg/d RIS 35 mg/wk	Oral	VID 200 IU CAL 500 mg	290
Luckey 2003	-	1 year	Primary	Age 40 to 70 yrs, postmenopausal 6-12 months, LS and FN BMD T-score between 2.5 and 1.0, no spine or hip osteoporotic fracture.	56.2 (5.9)	-	0%	ALE 5 mg/d ALE 35 mg/wk	Oral	VID 250 IU CAL 500 mg	723
McClung 2012	-	2 years	Secondary	Age > 50 yrs, ambulatory, good health, postmenopausal ≥ 5 yrs, LS or TH BMD T-score < −2.5 or T-score < −2 with at least one prevalent vertebral fracture.	65.6 (7.4)	-3.1 (0.2)	26%	RIS 5 mg/d RIS 35 mg/wk RIS 35 mg/wk	Oral	VID 800-1000 IU CAL 1000 mg	922
Schnitzer 2000	-	1 year	Secondary	Age 40 to 90 yrs, postmenopausal ≥2 yrs, with LS and/or FN BMD T-score ≤-2.5 or history of osteoporotic fracture.	66.5	-	17%	ALE 10 mg/d ALE 70 mg/wk ALE 35 mg x2/wk	Oral	VID 250 IU CAL 500 mg	1258

*Abbreviations: BMD=bone mineral density, SD=standard deviation, m=months, yr=year, d=day, wk=week. ALE=alendronate, RIS=risedronate, VID=vitamin D, CAL=calcium, IU=international units.

Figure 4.1: PRISMA flow diagram for network meta-analyses



** 83 studies and 82 records were included in network meta-analyses because Reginster et al. (120) reported data for two trials in the same publication.*

4.3.2 RISK OF BIAS

Four studies were assessed as low risk of bias across all domains (91, 127-129) while no study had high risk of bias across all domains. Approximately half of the trials had low (37/83, 45%) or unclear risk of bias (45/83, 54%) for random sequence generation. Nineteen studies had low risk of bias for allocation concealment, but three-quarter of studies (62/83, 75%) had unclear risk of bias for allocation concealment due to insufficient information provided in the reports. Seventeen studies (20%) scored low risk of bias for both domains. One study had high risk of bias for both random sequence generation and allocation concealment because participants were randomized “in the order of recruitment” (93).

Blinding was assessed separately for objective and subjective outcomes. All studies had low risk of bias for objective outcomes. Twenty-eight studies (34%) had low risk of bias for subjective outcomes, 25 studies (30%) had high risk of bias, and 23 studies (28%) had unclear risk based on a lack of information describing blinding. Seven studies did not report any subjective outcomes thus the domain was not applicable to the studies.

Incomplete outcome data was assessed separately for efficacy and safety outcomes. For efficacy outcomes, the completion rate at the end of trial was calculated by dividing the number of participants that completed the trial by the total number randomized. If more than 80% of participants completed the trial, and the reasons and rates of withdrawal were balanced across groups, the study was judged low risk of bias. For safety outcomes, differential withdrawal due to adverse events was also considered. Forty-four studies (53%) had low risk of bias for efficacy outcomes, 29 studies (35%) had high risk of bias, and 10 studies had unclear risk of bias (12%). Forty-four (53%) studies had low risk of bias for safety outcomes, 27 studies (33%) had high risk of bias, and 9 studies (11%) had unclear risk of bias. The domain was not applicable in 3 studies that only contained efficacy outcomes. Overall, 44 studies (53%) had low risk of bias for both efficacy and safety outcomes, 27 (33%) had high risk of bias for both, and 9 (11%) trials had unclear risk of bias in both domains due to not reporting enough information to assess the total completion rate.

Selective reporting was assessed by hierarchically examining the protocol, clinical trial record databases, methods, and abstract of studies included in the analysis. Sixty-five studies had low risk of bias in this domain. High risk of bias was given to three studies. One study contained a control group that discontinued at the second year of a three-year trial but only end of trial results for fracture were reported (130). Another publication (120) reported on two trials in one publication (counted as two separate studies in analysis and in the PRISMA diagram): Study Non-Fx and Study Fx. Both studies listed incidence of new vertebral fractures as a primary or secondary outcome, but results were only reported for Study Fx. In Study Non-Fx, the authors commented that a significant difference between the treatment groups was not found but did not provide numerical data. Non-vertebral fractures were reported as adverse events only in Study Non-Fx and not in Study Fx, although this outcome was not listed as a pre-specified outcome in either. These two studies may have potential for high risk of bias since data was likely available for the outcome of interest but was not reported in any of the published sources we found. Potential for other sources of bias was mostly judged as low (64/83, 77%), followed by high (12/83, 15%) and unclear (7/83, 8%) risk of bias. Studies with discontinued arms due to protocol changes without sufficient explanation were prone to high risk of bias in this domain.

Figure 4.2: Summary risk of bias assessments

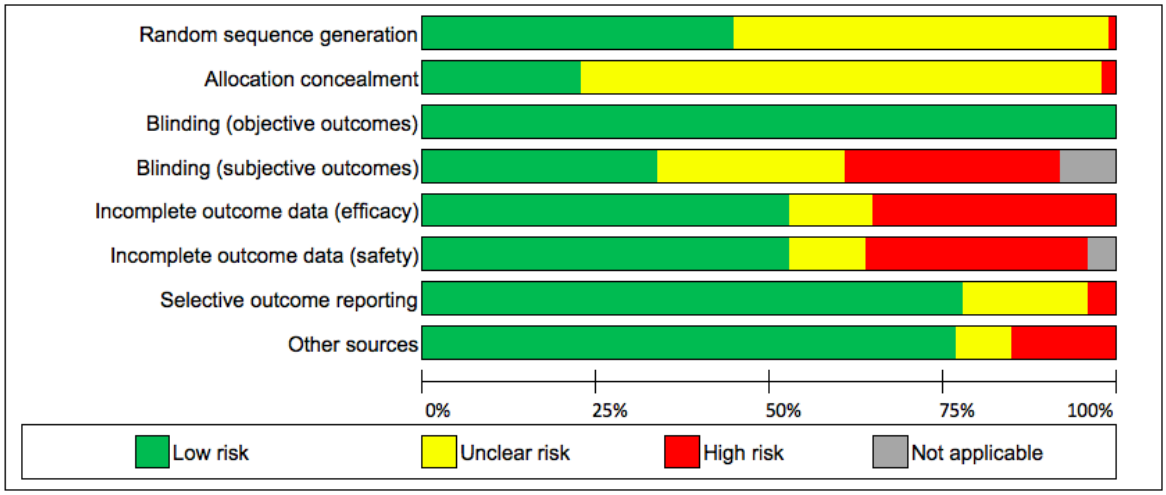


Table 4.7: Risk of bias assessments for 83 studies

Study	Random sequence generation	Allocation concealment	Blinding (objective outcomes)	Blinding (subjective outcomes)	Incomplete outcome data (efficacy outcomes)	Incomplete outcome data (safety outcomes)	Selective reporting	Other sources
Adami 2008	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Akyol 2006	Unclear	Unclear	Low	NA	High	High	Unclear	Unclear
Ascott-Evans 2003	Low	Low	Low	Low	Low	Low	Low	Low
Bai 2013	Unclear	Unclear	Low	High	Unclear	Unclear	Low	Low
Black 1996	Low	Low	Low	Low	Low	Low	Low	High
Black 2007	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Black 2012	Low	Low	Low	Low	Low	Low	Unclear	Low
Black 2015	Low	Low	Low	Low	Low	Low	Low	Low
Black 2006	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low
Bock 2012	Low	Low	Low	Low	Low	Low	Low	Low
Bone 1997	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
Bone 2000	Low	Unclear	Low	Unclear	High	High	Low	Low
Braga 2003	Low	Low	Low	High	High	High	Unclear	Low
Cascella 2005	Unclear	Unclear	Low	High	Low	Low	Low	Low
Chavez-Valencia 2014	Low	Unclear	Low	NA	Low	Low	Low	Low
Chesnut 1995	Unclear	Unclear	Low	High	Low	Low	Low	Low
Chesnut 2004	Low	Unclear	Low	Low	High	High	Low	Low
Cosman 2011	Low	Low	Low	High	Low	Low	Low	Low
Cummings 1998	Low	Low	Low	Low	Low	Low	Low	High
Delmas 2006	Low	Low	Low	Unclear	High	High	Low	Low
Dursun 2001	Unclear	Unclear	Low	High	Unclear	Unclear	Low	Low
Eviö 2004	Unclear	Unclear	Low	Low	High	High	Low	Low
Fogelman 2000	Unclear	Unclear	Low	High	High	High	Low	Low
Galesanu 2011	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	High
Greenspan 1998	Unclear	Unclear	Low	Unclear	High	High	Low	High
Greenspan 2002	Low	Unclear	Low	Low	Unclear	Unclear	Low	Low
Grey 2012	Low	Low	Low	Low	Low	Low	Low	Low
Hadji 2012	Low	Unclear	Low	High	High	High	Unclear	Low
Hagino 2009	Low	Unclear	Low	Low	Low	Low	Low	Low

Study	Random sequence generation	Allocation concealment	Blinding (objective outcomes)	Blinding (subjective outcomes)	Incomplete outcome data (efficacy outcomes)	Incomplete outcome data (safety outcomes)	Selective reporting	Other sources
Harris 1999	Low	Low	Low	Low	High	High	Low	Low
Herd 1997	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Hooper 2005	Low	Low	Low	Low	High	High	Low	Low
Hosking 1998	Unclear	Low	Low	High	Low	Low	Low	Low
Ishida 2004	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Iwamoto 2005	High	High	Low	High	Low	Low	Low	Low
Jokar 2016	Unclear	Unclear	Low	High	Unclear	Unclear	Unclear	Unclear
Kasukawa 2014	Unclear	High	Low	High	High	High	Low	Low
Lees 1996	Unclear	Unclear	Low	Unclear	High	High	Low	Low
Leung 2005	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Lewiecki 2007	Unclear	Unclear	Low	High	Low	Low	Unclear	Low
Li 2005	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low
Liang 2017	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Low
Liberman 1995	Low	Unclear	Low	Low	Low	Low	Low	Low
Lyritis 1997	Unclear	Unclear	Low	High	High	High	Low	Low
Matsumoto 2009	Low	Low	Low	Unclear	High	High	Low	Low
McCloskey 2004	Low	Unclear	Low	Low	High	High	Low	Low
McClung 1998	Low	Unclear	Low	Low	High	High	Low	Low
McClung 2009	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
McClung 2001	Unclear	Unclear	Low	Low	High	High	Low	High
Meunier 1997	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Michalska 2006	Unclear	Unclear	Low	High	Low	Low	Low	Low
Miller 2008	Low	Low	Low	Low	Low	Low	Low	Low
Montessori 1997	Low	Unclear	Low	High	High	High	Unclear	Unclear
Mortensen 1998	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Murphy 2001	Unclear	Unclear	Low	NA	High	NA	Low	Unclear
Nakamura 2014	Unclear	Low	Low	High	Low	Low	Unclear	High
Nakamura 2017	Low	Unclear	Low	High	High	High	Low	Low
Orimo 2011	Low	Low	Low	High	High	High	Low	Unclear
Palomba 2002	Low	Unclear	Low	Unclear	Low	Low	Low	Low

Study	Random sequence generation	Allocation concealment	Blinding (objective outcomes)	Blinding (subjective outcomes)	Incomplete outcome data (efficacy outcomes)	Incomplete outcome data (safety outcomes)	Selective reporting	Other sources
Palomba 2005	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Pols 1999	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Pouilles 1997	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Reginster 2006	Low	Low	Low	Low	Low	Low	Unclear	Low
Reginster 2001 (Study Non-Fx)	Unclear	Unclear	Low	Unclear	Low	Low	High	Unclear
Reginster 2001 (Study Fx)	Unclear	Unclear	Low	Unclear	High	High	High	High
Reginster 2000	Unclear	Unclear	Low	Unclear	High	High	Low	Low
Robles-Carranza 2013	Unclear	Unclear	Low	High	High	High	Unclear	Unclear
Rossini 1999	Unclear	Unclear	Low	High	High	High	High	High
Russo 1996	Unclear	Unclear	Low	High	Unclear	Unclear	Low	Low
Sarioglu 2006	Unclear	Unclear	Low	NA	Unclear	Unclear	Low	Low
Shiota 2001	Unclear	Unclear	Low	NA	Unclear	NA	Low	High
Storm 1990	Low	Unclear	Low	Unclear	High	High	Low	High
Tan 2016	Low	Unclear	Low	High	Low	Low	Unclear	Low
Tanakol 2007	Unclear	Unclear	Low	High	High	High	Low	High
Välimäki 2007	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Low
Watts 1990	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Wimalawansa 1998	Low	Unclear	Low	High	Low	Low	Low	Low
Yan 2009	Low	Unclear	Low	Low	Low	Low	Low	Low
Yang 2015	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Fukunaga 2002	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Qin 2007	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Nakamura 2013	Low	Low	Low	NA	Low	Low	Low	Low
Pacifici 1988	Unclear	Unclear	Low	NA	High	NA	Low	High

4.3.3 CHARACTERISTICS OF OUTCOMES

The total number of studies included for each outcome varied. The most commonly reported outcome was non-vertebral fractures whose network meta-analysis included 43 studies. Wrist fractures were the least frequently reported outcome, and the analysis only included 9 studies. Network meta-analyses using random-effects models with three chains, 10000 iterations and 10000 burn-in iterations were conducted for all efficacy outcomes and all safety outcomes except jaw osteonecrosis, atrial fibrillation, and atypical femoral fracture.

Inconsistency plots are shown in Appendix 7. All network meta-analyses adhered to assumptions underlying the method except four networks that showed evidence of inconsistency (main analyses of radiographic vertebral, non-vertebral and wrist fracture; secondary prevention subgroup analysis of radiographic vertebral fracture). Investigation of potential causes for inconsistency within closed loops such as uneven distribution of effect modifiers among studies and sensitivity analyses excluding inconsistent studies are presented in Appendix 8.

For each efficacy or safety outcome, results of the main analysis will be described, followed by results of the subgroup analysis, and then the sensitivity analysis. Network diagrams for subgroup analyses of treatment durations are presented in Appendix 9. Sensitivity analyses are summarized descriptively in the main text, and tables of results will be provided in Appendix 10.

Table 4.8: Summary of included studies by outcome

	Radio vertebral fractures	Clinical vertebral fractures	Non-vertebral fractures	Hip fractures	Wrist fractures	Quality of life	Withdrawal due to adverse events	Serious adverse events	GI adverse events	Acute phase response
Number of trials	32	11	43	15	9	2	35	27	32	6
Number of treatment nodes	21	11	21	7	5	3	21	14	15	5
Number of participants	26717	15594	45779	31544	12005	2004	26490	34452	34805	8595
Number of 2-arm trials	24	8	36	15	9	2	29	20	26	5
Number of 3-arm trials	8	3	7	0	0	0	6	7	6	0
Number of 4-arm trials	0	0	0	0	0	0	0	0	0	1

Abbreviations: Radio=radiographic, GI=gastrointestinal.

4.3.4 RADIOGRAPHIC VERTEBRAL FRACTURES

4.3.4.1 MAIN ANALYSIS

The network meta-analysis for radiographic vertebral fractures included 32 studies, 21 treatments and 26717 participants (80, 84-87, 90, 94, 95, 117, 120-122, 124, 125, 131-148). Two were primary prevention trials, and 30 were secondary prevention studies. Three trials included men (84, 121, 122), but results were reported separately for both sexes. Study durations ranged from 48 weeks (121) to 5 years (87). The most common comparison was between alendronate 10 mg/day and placebo. Of the thirty-two trials, twenty were two-arm, placebo-controlled trials, four were two-arm, head-to-head trials, seven were three-arm, placebo-controlled studies, and one was a three-arm, head-to-head study.

Ten of twenty-one treatments were significantly better statistically than placebo at preventing radiographic vertebral fractures (Table 4.9). These included 8 treatments of single bisphosphonates compared to placebo: two doses of alendronate (5, 10 mg/day), two doses of etidronate (200, 400 mg/day), risedronate (5 mg/day), ibandronate (2.5 mg/day), zoledronic acid (5 mg/year) and minodronate (1 mg/day). Two combination treatments were significantly better statistically than placebo: etidronate 400 mg/day plus hormone replacement therapy and etidronate 400 mg/day combined with phosphate 2 mg/day. Effect estimates are lowest for zoledronic acid and highest for alendronate 5 mg/day. Participants taking one of the ten treatments listed above have a range of 46% (alendronate 5 mg/day, 95% CrI: 0.31, 0.93) to 73% (zoledronic acid, 95% CrI: 0.18, 0.43) statistically significant reduction in odds of sustaining a vertebral fracture compared to patients taking placebo.

Head-to-head comparisons of bisphosphonates showed that zoledronic acid 5 mg/year is significantly better statistically than clodronate 800 mg/day (OR 0.43, 95% CrI: 0.20, 0.93), alendronate 10 mg/day (OR 0.46, 95% CrI: 0.29, 0.80) and risedronate 5 mg/day (OR 0.51, 95% CrI: 0.31, 0.92). Patients taking zoledronic acid have statistically significant 57% reduction compared to

those taking clodronate, 54% reduced odds of sustaining a radiographic vertebral fracture compared to those taking alendronate, and 49% reduction compared to those taking risedronate.

Among unapproved bisphosphonates, neridronate was not significantly different from placebo or any other intervention. Both doses of tiludronate (350 mg and 1400 mg per month) were significantly worse statistically than 6 treatments at fracture prevention: etidronate 200 mg/day, etidronate 400 mg/day with HRT, etidronate 400 mg/day with phosphate, risedronate 5 mg/day, zoledronic acid 5 mg/year, minodronate 1 mg/day. In addition, tiludronate 350 mg/month was also significantly worse than alendronate 10 mg/day, etidronate 400 mg/day, and ibandronate 2.5 mg/day.

Combination treatments for alendronate, etidronate and risedronate were not significantly superior statistically compared to single bisphosphonates. Alfacalcidol 1 µg/day added to alendronate 5 mg/day resulted in a statistically non-significant 9% reduction in odds of fracture compared to alendronate alone (OR 0.91, 95% CrI: 0.55, 1.52). Similarly, HRT added to alendronate 10 mg/day resulted in a statistically non-significant 7% increase in odds of fracture compared to alendronate 10 mg/day alone (OR 1.07, 95% CrI: 0.32, 3.95). Etidronate combined with HRT resulted in a statistically non-significant 77% reduction in odds compared to etidronate alone (OR 0.23, 95% CrI: 0.01, 1.79), while combination with phosphate 2 g/day showed a non-significant 45% reduction in odds (OR 0.55, 95% CrI: 0.12, 1.99). Risedronate 2.5 mg/day combined with vitamin K (menatetrenone) 45 mg/day was worse than risedronate alone (OR 1.55, 95% CrI: 0.29, 7.71).

Inconsistency between estimates was found in the etidronate and risedronate arms of Fukunaga et al. (2002). Potential causes of inconsistency may be a shorter duration and the inclusion of two men within the risedronate group (Appendix 8). A sensitivity analysis excluding the study showed greater efficacy of etidronate and lower efficacy of risedronate compared to current results (Appendix 8). Additionally, etidronate showed greater efficacy than alendronate 10 mg/day, and risedronate became significantly worse than zoledronic acid and minodronate. Changes in significance occurred due to narrowing of credible intervals, but direct of effects did not change.

Figure 4.3: Network diagram for radiographic vertebral fractures

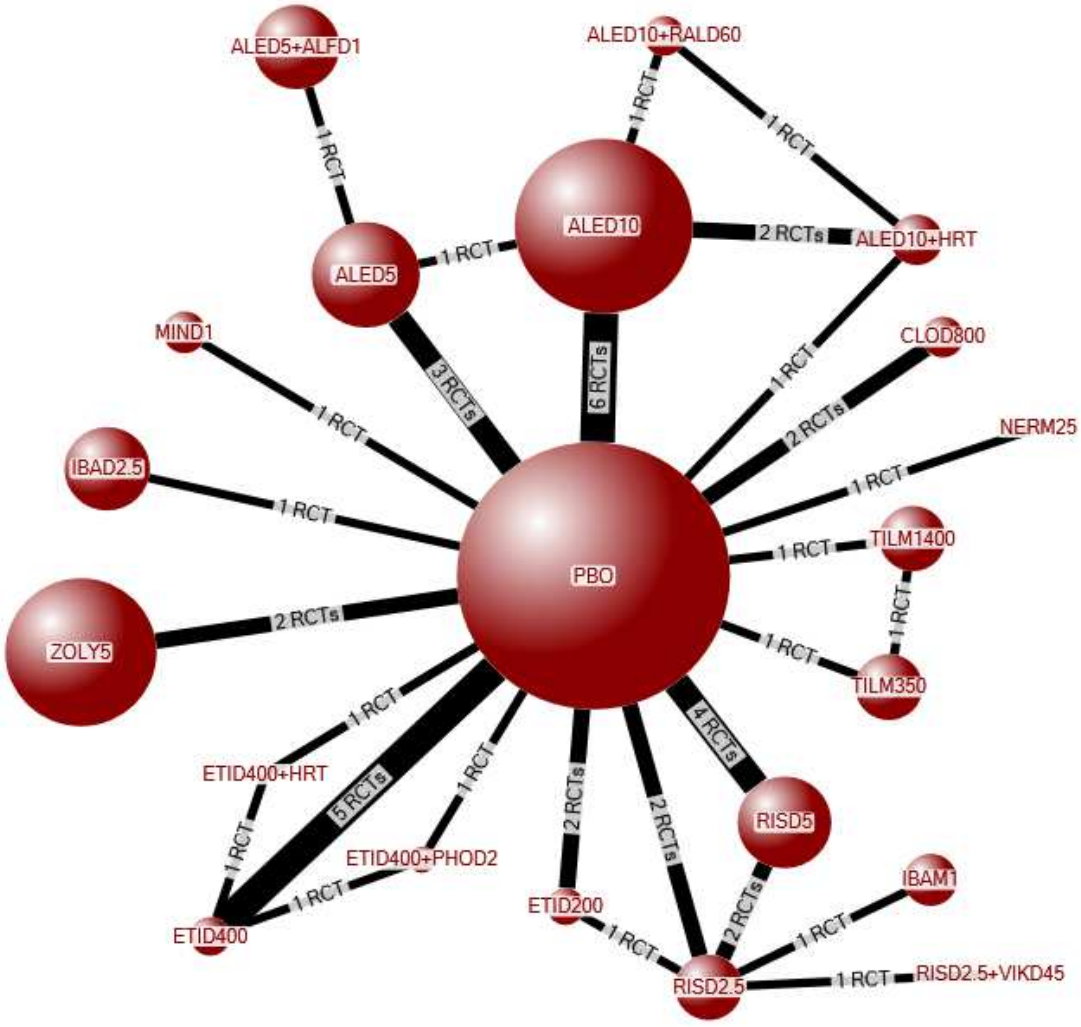


Table 4.9: Staircase diagram for radiographic vertebral fractures

PBO	**PBO**																				
ALED5	**0.54 (0.31,0.93)**	**ALED5**																			
ALED5 +ALFD1	0.49 (0.23,1.05)	0.91 (0.55,1.52)	**ALED5 +ALFD1**																		
ALED10	**0.58 (0.44,0.76)**	1.08 (0.59,1.94)	1.19 (0.53,2.53)	**ALED10**																	
ALED10 +HRT	0.61 (0.19,2.30)	1.13 (0.31,4.69)	1.25 (0.31,5.64)	1.07 (0.32,3.95)	**ALED10 +HRT**																
ALED10 +RALD60	0.15 (0.01,1.19)	0.28 (0.02,2.53)	0.31 (0.02,2.93)	0.27 (0.01,2.07)	0.24 (0.01,1.77)	**ALED10 +RALD60**															
ETID200	**0.31 (0.13,0.68)**	0.57 (0.22,1.49)	0.64 (0.21,1.82)	0.53 (0.22,1.24)	0.51 (0.11,2.05)	2.00 (0.23,35.51)	**ETID200**														
ETID400	**0.44 (0.21,0.89)**	0.82 (0.33,2.01)	0.89 (0.31,2.52)	0.76 (0.35,1.65)	0.73 (0.16,2.66)	2.97 (0.32,52.54)	1.42 (0.47,4.16)	**ETID400**													
ETID400 +HRT	**0.10 (0.005,0.71)**	0.19 (0.01,1.50)	0.21 (0.01,1.80)	0.18 (0.01,1.26)	0.16 (0.01,1.62)	0.65 (0.02,22.52)	0.33 (0.01,2.74)	0.23 (0.01,1.79)	**ETID400 +HRT**												
ETID400 +PHOD2	**0.24 (0.05,0.80)**	0.45 (0.09,1.63)	0.50 (0.08,1.96)	0.42 (0.08,1.44)	0.40 (0.04,2.33)	1.64 (0.10,35.98)	0.78 (0.13,3.32)	0.55 (0.12,1.99)	2.30 (0.21,80.52)	**ETID400 +PHOD2**											
RISD2.5	0.75 (0.29,1.55)	1.39 (0.48,3.42)	1.53 (0.46,4.27)	1.29 (0.49,2.82)	1.18 (0.24,5.04)	4.80 (0.50,99.65)	2.36 (0.78,6.94)	1.67 (0.54,4.94)	7.15 (0.79,174.80)	3.08 (0.62,16.66)	**RISD2.5**										
RISD2.5 +VIKD45	1.12 (0.19,6.85)	2.06 (0.32,13.33)	2.26 (0.33,15.38)	1.95 (0.31,12.26)	1.83 (0.17,15.55)	7.77 (0.46,233.10)	3.56 (0.58,25.08)	2.58 (0.36,17.94)	11.39 (0.54,364.20)	4.71 (0.52,45.30)	1.55 (0.29,7.71)	**RISD2.5 +VIKD45**									
RISD5	**0.53 (0.38,0.73)**	0.98 (0.51,1.86)	1.09 (0.47,2.39)	0.91 (0.59,1.39)	0.86 (0.22,2.97)	3.40 (0.44,64.67)	1.72 (0.71,4.11)	1.20 (0.55,2.73)	5.07 (0.73,110.30)	2.16 (0.62,11.07)	0.71 (0.33,1.81)	0.47 (0.08,2.90)	**RISD5**								
IBAD2.5	**0.49 (0.28,0.84)**	0.91 (0.42,1.94)	1.00 (0.39,2.46)	0.84 (0.45,1.54)	0.79 (0.19,3.05)	3.22 (0.38,58.62)	1.58 (0.60,4.25)	1.11 (0.45,2.74)	4.76 (0.61,107.60)	2.00 (0.53,10.61)	0.65 (0.26,1.94)	0.44 (0.06,2.79)	0.92 (0.49,1.76)	**IBAD2.5**							
IBAM1	0.63 (0.21,1.57)	1.19 (0.34,3.35)	1.29 (0.34,4.07)	1.09 (0.35,2.81)	1.00 (0.18,4.85)	4.11 (0.39,93.75)	2.01 (0.58,6.60)	1.41 (0.40,4.77)	6.05 (0.64,148.90)	2.65 (0.47,15.25)	0.84 (0.48,1.51)	0.54 (0.10,3.11)	1.20 (0.39,3.04)	1.30 (0.38,3.79)	**IBAM1**						
ZOLY5	**0.27 (0.18,0.43)**	0.50 (0.26,1.02)	0.55 (0.24,1.31)	**0.46 (0.29,0.80)**	0.45 (0.11,1.61)	1.76 (0.22,32.75)	0.88 (0.37,2.25)	0.61 (0.28,1.44)	2.62 (0.36,57.26)	1.11 (0.31,5.70)	0.36 (0.16,1.03)	0.24 (0.04,1.58)	**0.51 (0.31,0.92)**	0.55 (0.29,1.14)	0.43 (0.16,1.43)	**ZOLY5**					
MIND1	**0.19 (0.05,0.56)**	0.35 (0.08,1.21)	0.38 (0.08,1.46)	0.33 (0.08,1.03)	0.30 (0.04,1.68)	1.23 (0.11,24.92)	0.60 (0.12,2.42)	0.43 (0.09,1.52)	1.86 (0.17,46.32)	0.75 (0.14,5.17)	0.25 (0.06,1.04)	0.17 (0.02,1.40)	0.36 (0.09,1.16)	0.39 (0.09,1.34)	0.29 (0.06,1.35)	0.69 (0.17,2.24)	**MIND1**				
CLOD800	0.63 (0.33,1.20)	1.17 (0.50,2.70)	1.29 (0.48,3.37)	1.09 (0.54,2.17)	1.01 (0.23,4.07)	4.16 (0.47,81.53)	2.04 (0.70,5.88)	1.44 (0.54,3.73)	6.03 (0.80,130.80)	2.58 (0.67,14.09)	0.84 (0.32,2.59)	0.55 (0.08,3.94)	1.19 (0.58,2.50)	1.28 (0.56,3.05)	0.99 (0.33,3.57)	**2.31 (1.07,4.95)**	3.36 (0.94,14.80)	**CLOD800**			
NERM25	0.26 (0.02,2.66)	0.48 (0.03,5.62)	0.53 (0.03,6.24)	0.45 (0.03,4.69)	0.41 (0.02,5.14)	1.87 (0.05,45.24)	0.83 (0.05,10.47)	0.60 (0.03,7.16)	2.74 (0.06,109.70)	1.08 (0.05,19.57)	0.35 (0.02,4.45)	0.23 (0.01,4.48)	0.50 (0.03,5.10)	0.53 (0.03,5.63)	0.41 (0.02,5.78)	0.97 (0.06,10.11)	1.43 (0.07,18.85)	0.41 (0.02,4.57)	**NERM25**		
TILM350	1.11 (0.69,1.77)	2.06 (0.99,4.18)	2.28 (0.92,5.38)	**1.92 (1.12,3.27)**	1.81 (0.46,6.44)	7.22 (0.88,136.90)	**3.61 (1.40,9.18)**	**2.50 (1.08,5.88)**	**10.58 (1.47,237.90)**	**4.54 (1.25,23.51)**	1.48 (0.62,4.16)	0.98 (0.15,6.20)	**2.10 (1.18,3.71)**	**2.27 (1.11,4.64)**	1.75 (0.63,5.73)	**4.13 (2.08,7.38)**	**5.88 (1.80,24.44)**	1.77 (0.79,3.88)	4.24 (0.40,69.26)	**TILM350**	
TILM1400	1.02 (0.63,1.61)	1.89 (0.89,3.85)	2.08 (0.83,4.92)	1.75 (1.00,2.99)	1.66 (0.41,5.90)	6.56 (0.80,129.10)	**3.29 (1.28,8.45)**	2.31 (0.98,5.37)	**9.67 (1.35,224.30)**	**4.13 (1.16,21.94)**	1.35 (0.57,3.84)	0.90 (0.14,5.63)	**1.93 (1.07,3.41)**	2.08 (1.00,4.27)	1.60 (0.58,5.23)	**3.79 (1.89,6.75)**	**5.38 (1.64,21.94)**	1.62 (0.72,3.53)	3.90 (0.36,62.76)	0.92 (0.57,1.46)	**TILM1400**

Bolded results are statistically significant. Green cells with bolded black font indicate significant preventive effect or lower odds of adverse event, red cells with white bolded font indicate significant harmful effect or higher odds of adverse event. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, RALD60=raloxifene 60 mg/day, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, HRT=hormone replacement therapy, RISD2.5=risedronate 2.5 mg/day, VIKD45=vitamin K 45 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM1=ibandronate 1 mg/month, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, NERM25=neridronate 25 mg/month, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

4.3.4.2 SUBGROUP ANALYSES

Primary and secondary prevention

Thirty of thirty-two studies were classified as secondary prevention studies and two studies were classified as primary prevention (85, 140). A network could not be conducted for primary prevention studies because one of the studies had zero events in all arms and could not contribute to analysis (140).

A network including only secondary prevention studies (total 22471 participants) showed all ten treatments previously found to be significantly better than placebo remained statistically significant. Zoledronic acid remains significantly better statistically than alendronate 10 mg/day and clodronate 800 mg/day, but no longer better than risedronate 5 mg/day (OR 0.51, 95% CrI: 0.30, 1.03). Three additional treatments showed statistically significant efficacy in the subgroup analysis but were not significant in the main analysis: oral alendronate 10 mg/day combined with raloxifene 60 mg/day compared to placebo (OR 0.16, 95% CrI: 0.01, 0.98), intravenous ibandronate 1 mg/month compared to placebo (OR 0.45, CrI: 0.21, 0.93), and oral minodronate 1 mg/day compared to alendronate 10 mg/day (OR 0.31, 95% CrI: 0.08, 0.99). All three treatments contain direct evidence from only one study each, and effect estimates were previously close to significance in the main analysis. Among unapproved bisphosphonates, neridronate 25 mg monthly remains not significantly better than placebo or other treatments, and oral tiludronate remains inferior to most treatments.

Due to many overlapping studies with the main analysis, inconsistency was also found between the etidronate and risedronate arms of Fukunaga et al. (2002). Potential causes of inconsistency are likely similar to reasons suggested in the main analysis (*i.e.,* shorter duration, inclusion of men in the risedronate group) (Appendix 8), and results of the sensitivity analysis also showed greater efficacy of etidronate and lower efficacy of risedronate compared to the current analysis (Appendix 8).

Figure 4.4: Network diagram for radiographic vertebral fractures (secondary prevention)

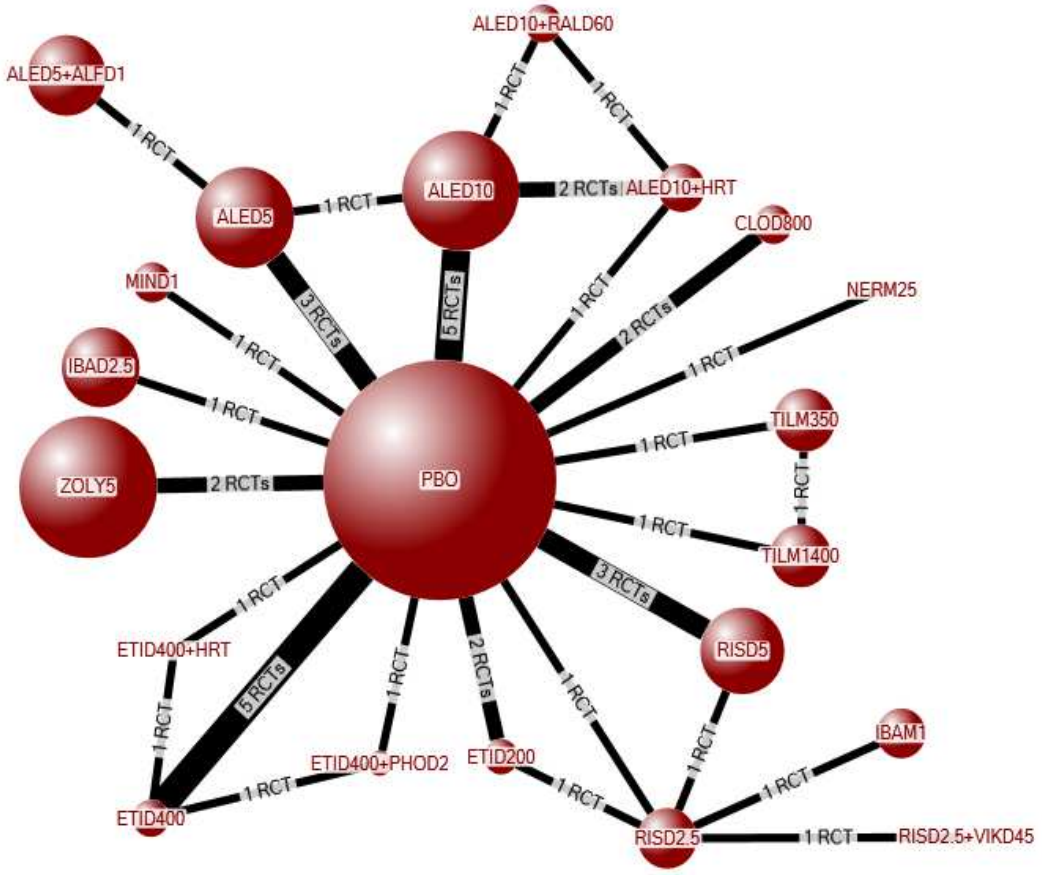


Table 4.10: Staircase diagram for radiographic vertebral fractures (secondary prevention)

PBO	**PBO**																				
ALED5	**0.56 (0.31,0.94)**	**ALED5**																			
ALED5 +ALFD1	0.51 (0.22,1.11)	0.92 (0.52,1.63)	**ALED5 +ALFD1**																		
ALED10	**0.59 (0.42,0.83)**	1.07 (0.57,2.06)	1.17 (0.50,2.73)	**ALED10**																	
ALED10 +HRT	0.63 (0.17,2.18)	1.14 (0.29,4.23)	1.24 (0.28,5.04)	1.06 (0.30,3.59)	**ALED10 +HRT**																
ALED10 +RALD60	**0.16 (0.01,0.98)**	0.29 (0.01,2.04)	0.31 (0.02,2.44)	0.27 (0.01,1.67)	0.26 (0.01,1.64)	**ALED10 +RALD60**															
ETID200	**0.31 (0.13,0.70)**	0.55 (0.21,1.58)	0.61 (0.20,1.92)	0.52 (0.21,1.25)	0.49 (0.12,2.21)	2.00 (0.24,40.90)	**ETID200**														
ETID400	**0.45 (0.23,0.87)**	0.82 (0.34,1.99)	0.89 (0.31,2.54)	0.77 (0.36,1.57)	0.71 (0.18,3.07)	2.86 (0.41,58.19)	1.47 (0.50,4.28)	**ETID400**													
ETID400 +HRT	**0.13 (0.01,0.82)**	0.23 (0.01,1.64)	0.25 (0.02,1.88)	0.22 (0.01,1.43)	0.20 (0.01,2.21)	0.85 (0.03,23.55)	0.42 (0.02,3.06)	0.28 (0.02,1.84)	**ETID400 +HRT**												
ETID400 +PHOD2	**0.25 (0.06,0.88)**	0.46 (0.10,1.80)	0.50 (0.10,2.14)	0.43 (0.09,1.58)	0.41 (0.06,2.24)	1.63 (0.16,38.64)	0.81 (0.16,3.69)	0.56 (0.13,2.00)	1.96 (0.20,39.99)	**ETID400 +PHOD2**											
RISD2.5	0.68 (0.23,1.67)	1.23 (0.35,3.68)	1.34 (0.34,4.49)	1.15 (0.38,2.98)	1.09 (0.22,5.53)	4.28 (0.50,98.78)	2.18 (0.66,6.74)	1.49 (0.43,4.71)	5.24 (0.61,92.40)	2.68 (0.51,14.67)	**RISD2.5**										
RISD2.5 +VIKD45	0.99 (0.15,7.27)	1.78 (0.25,14.30)	1.94 (0.26,17.37)	1.68 (0.24,12.65)	1.62 (0.17,17.66)	6.86 (0.43,210.00)	3.24 (0.45,27.75)	2.24 (0.29,17.60)	7.94 (0.52,205.00)	4.03 (0.39,45.76)	1.51 (0.26,8.85)	**RISD2.5 +VIKD45**									
RISD5	**0.53 (0.36,0.75)**	0.96 (0.49,1.90)	1.05 (0.44,2.52)	0.90 (0.53,1.45)	0.85 (0.23,3.28)	3.35 (0.51,65.54)	1.71 (0.70,4.28)	1.17 (0.55,2.51)	4.05 (0.61,64.52)	2.08 (0.56,9.70)	0.78 (0.31,2.29)	0.53 (0.07,3.56)	**RISD5**								
IBAD2.5	**0.48 (0.26,0.88)**	0.87 (0.39,2.00)	0.95 (0.35,2.62)	0.82 (0.41,1.62)	0.77 (0.19,3.20)	3.07 (0.43,60.45)	1.56 (0.57,4.42)	1.07 (0.43,2.66)	3.68 (0.53,62.55)	1.91 (0.46,9.28)	0.71 (0.24,2.48)	0.48 (0.06,3.58)	0.91 (0.45,1.88)	**IBAD2.5**							
IBAM1	**0.45 (0.21,0.93)**	0.82 (0.32,2.07)	0.90 (0.30,2.62)	0.77 (0.34,1.70)	0.72 (0.17,3.19)	2.88 (0.39,58.06)	1.47 (0.49,4.44)	1.00 (0.36,2.71)	3.47 (0.47,58.84)	1.77 (0.42,9.61)	0.67 (0.22,2.34)	0.46 (0.05,3.33)	0.85 (0.45,1.61)	0.94 (0.35,2.39)	**IBAM1**						
ZOLY5	**0.27 (0.18,0.47)**	0.49 (0.25,1.08)	0.54 (0.22,1.46)	**0.46 (0.27,0.88)**	0.44 (0.12,1.76)	1.75 (0.27,33.34)	0.89 (0.36,2.41)	0.60 (0.28,1.43)	2.11 (0.32,35.71)	1.08 (0.30,5.20)	0.41 (0.15,1.37)	0.28 (0.04,1.96)	0.51 (0.30,1.03)	0.57 (0.28,1.29)	0.60 (0.27,1.57)	**ZOLY5**					
MIND1	**0.18 (0.05,0.57)**	0.33 (0.08,1.18)	0.36 (0.08,1.45)	**0.31 (0.08,0.99)**	0.29 (0.05,1.64)	1.16 (0.13,25.87)	0.59 (0.13,2.48)	0.40 (0.09,1.52)	1.44 (0.14,28.50)	0.71 (0.12,4.83)	0.27 (0.05,1.35)	0.18 (0.02,1.84)	0.35 (0.09,1.15)	0.38 (0.09,1.36)	0.41 (0.09,1.56)	0.67 (0.15,2.20)	**MIND1**				
CLOD800	0.64 (0.33,1.30)	1.15 (0.49,2.92)	1.25 (0.46,3.74)	1.08 (0.51,2.35)	1.02 (0.26,4.37)	4.09 (0.58,81.25)	2.07 (0.72,6.24)	1.41 (0.56,3.78)	4.95 (0.70,88.65)	2.54 (0.61,13.02)	0.94 (0.31,3.49)	0.63 (0.08,5.17)	1.20 (0.57,2.73)	1.32 (0.54,3.42)	1.41 (0.53,4.03)	**2.32 (1.01,5.22)**	3.49 (0.94,16.07)	**CLOD800**			
NERM25	0.23 (0.01,2.44)	0.43 (0.02,4.54)	0.46 (0.02,5.37)	0.40 (0.02,4.18)	0.36 (0.02,5.33)	1.44 (0.06,66.41)	0.74 (0.04,9.95)	0.50 (0.03,5.94)	1.79 (0.06,62.29)	0.92 (0.05,14.76)	0.33 (0.02,4.97)	0.23 (0.01,5.20)	0.44 (0.02,4.74)	0.47 (0.02,5.36)	0.50 (0.03,5.93)	0.83 (0.04,9.07)	1.28 (0.05,17.85)	0.37 (0.02,4.28)	**NERM25**		
TILM350	1.11 (0.65,1.89)	1.99 (0.94,4.47)	2.19 (0.84,5.88)	1.88 (0.98,3.49)	1.77 (0.47,7.15)	**7.11 (1.04,139.80)**	**3.59 (1.36,9.65)**	**2.43 (1.06,5.79)**	**8.54 (1.26,138.80)**	**4.30 (1.15,21.32)**	**1.64 (0.58,5.33)**	1.12 (0.13,8.20)	**2.09 (1.11,4.09)**	**2.30 (1.02,5.10)**	**2.44 (1.01,6.20)**	**4.08 (1.82,7.77)**	**6.04 (1.69,26.26)**	1.75 (0.69,3.95)	4.80 (0.43,89.10)	**TILM350**	
TILM1400	1.02 (0.59,1.72)	1.83 (0.85,4.10)	2.00 (0.77,5.27)	1.72 (0.90,3.22)	1.61 (0.42,6.59)	6.48 (0.95,130.00)	**3.30 (1.24,8.86)**	2.23 (0.95,5.30)	7.79 (1.15,129.40)	3.95 (1.05,19.46)	1.50 (0.53,4.91)	1.02 (0.13,7.56)	**1.91 (1.02,3.76)**	2.11 (0.93,4.73)	2.24 (0.91,5.63)	**3.74 (1.66,7.04)**	**5.52 (1.56,24.10)**	1.60 (0.64,3.61)	4.37 (0.39,84.51)	0.91 (0.53,1.57)	**TILM1400**

Green cellswith bolded black font indicate significant preventive effect or lower odds of adverse event, red cells with white bolded font indicate significant harmful effect or higher odds of adverse event. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, RALD60=raloxifene 60 mg/day, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, HRT=hormone replacement therapy, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, VIKD45=vitamin K 45 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM1=ibandronate 1 mg/month, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, NERM25=neridronate 25 mg/month, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Prior bisphosphonate experience

A network MA could not be conducted on studies with treatment-experienced participants, since only the FLEX study provided data for analysis, thus the data will be summarized descriptively. FLEX is an extension study for participants of the Fracture Intervention Trials (FIT) who received at least three years of alendronate 10 mg/day either during the trial or during the subsequent open-label extension period. The study duration of FLEX was five years. At the end of the study, the alendronate 10 mg/day arm had a lower rate of fracture (60/662, 9%) than the placebo arm (46/437, 10%).

A total of eleven studies included only bisphosphonate-naïve participants (10588 patients) with 11 treatments (80, 85, 87, 90, 94, 117, 137, 143, 146-148). Most comparisons are focused on alendronate and placebo (four studies). Ibandronate, minodronate and clodronate are directly compared in one study each. The years of publication ranged from 1990 to 2009, and study durations ranged from one to four years. Only one study was a head-to-head trial, all other studies were placebo-controlled trials.

Of the eleven treatments, five remained significantly better statistically than placebo as in the main analysis (alendronate 10 mg/day, etidronate 400 mg/day with HRT, etidronate 400 mg/day with phosphate, ibandronate 2.5 mg/day, and minodronate 1 g/day). Alendronate at 10 mg/day compared to placebo showed statistically significant reductions in odds of radiographic fracture for both the main analysis (OR 0.58, 95% CrI: 0.44, 0.76) and the subgroup analysis (OR 0.51, 95% CrI: 0.37, 0.70). A decreased odds ratio in the subgroup analysis suggests potential for greater alendronate efficacy in bisphosphonate-naïve populations, however the overlap in credible intervals indicates the difference is not significant compared to the main analysis where treatment-experienced women were also included.

Two treatments are no longer significantly better than placebo in the subgroup analysis due to a widening of 95% credible intervals (alendronate 5 mg/day and etidronate 400 mg/day). This may be attributed to fewer studies included in the subgroup analysis. In the main analysis, alendronate 5

mg/day was assessed in four studies and etidronate 400 mg/day was included five studies, whereas in the sensitivity both appeared in two studies each. The loss of study information and power in the subgroup analysis may have led to wider credible intervals and loss of significance.

Alendronate 10 mg/day combined with raloxifene 60 mg/day was previously not different than placebo in the main analysis (OR 0.15, 95% CrI: 0.01, 1.19), but became significantly better than placebo in the subgroup analysis (OR 0.11, 95% CrI: 0.01, 0.92).

Figure 4.5: Network diagram for radiographic vertebral fractures (bisphosphonate-naïve)

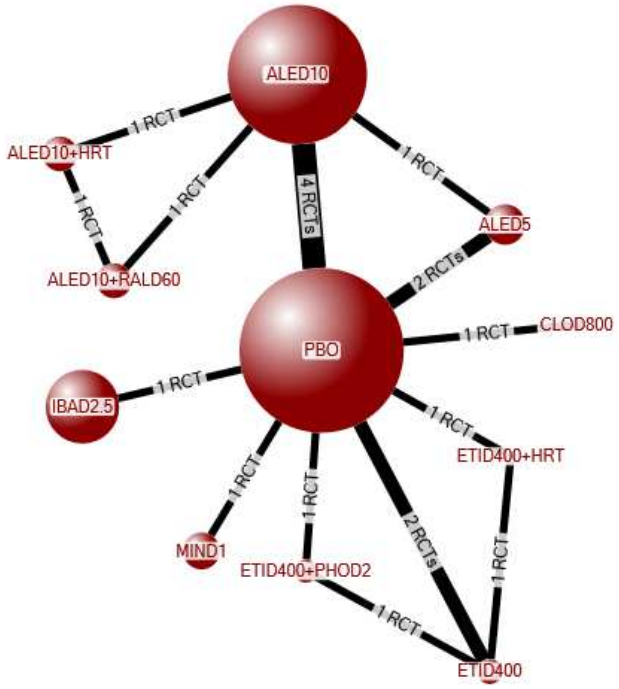


Table 4.11: Staircase diagram for radiographic vertebral fractures (bisphosphonate-naïve)

PBO	**PBO**									
ALED5	0.51 (0.23,1.06)	**ALED5**								
ALED10	**0.51 (0.37,0.70)**	0.99 (0.46,2.33)	**ALED10**							
ALED10 +HRT	0.39 (0.06,2.18)	0.76 (0.11,4.99)	0.76 (0.13,4.07)	**ALED10 +HRT**						
ALED10 +RALD60	**0.11 (0.01,0.92)**	0.21 (0.01,2.15)	0.21 (0.01,1.73)	0.26 (0.01,2.26)	**ALED10 +RALD60**					
ETID400	0.47 (0.18,1.20)	0.92 (0.27,3.29)	0.92 (0.33,2.42)	1.20 (0.15,9.30)	4.47 (0.43,102.3)	**ETID400**				
ETID400 +HRT	**0.12 (0.01,0.85)**	0.24 (0.01,1.87)	0.24 (0.01,1.73)	0.29 (0.01,5.01)	1.13 (0.04,37.28)	0.27 (0.02,1.97)	**ETID400 +HRT**			
ETID400 +PHOD2	**0.26 (0.06,0.91)**	0.50 (0.09,2.41)	0.51 (0.10,1.83)	0.65 (0.07,6.37)	2.53 (0.16,71.52)	0.55 (0.12,2.02)	2.09 (0.21,49.30)	**ETID400 +PHOD2**		
IBAD2.5	**0.48 (0.28,0.85)**	0.95 (0.38,2.50)	0.95 (0.50,1.77)	1.24 (0.20,8.45)	4.60 (0.50,91.76)	1.04 (0.35,3.07)	3.94 (0.52,67.65)	1.86 (0.48,9.58)	**IBAD2.5**	
MIND1	**0.19 (0.05,0.58)**	0.37 (0.08,1.42)	0.37 (0.09,1.18)	0.49 (0.05,3.89)	1.83 (0.15,48.66)	0.41 (0.07,1.74)	1.59 (0.14,32.16)	0.74 (0.11,4.82)	0.39 (0.09,1.34)	**MIND1**
CLOD800	2.72 (0.26,42.74)	5.37 (0.46,87.36)	5.26 (0.49,86.40)	7.13 (0.36,203.5)	**26.61 (1.07,2154)**	5.88 (0.47,98.58)	**24.81 (1.16,843.3)**	10.74 (0.73,248.2)	5.63 (0.51,91.88)	14.57 (0.90,288.4)

Green cellswith bolded black font indicate significant preventive effect or lower odds of adverse event, red cells with white bolded font indicate significant harmful effect or higher odds of adverse event. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, RALD60=raloxifene 60 mg/day, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, HRT=hormone replacement therapy, PHOD2=phosphate 2 g/day, IBAD2.5 =ibandronate 2.5 mg/day, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, NERM25=neridronate 25 mg/month, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Treatment durations

Whereas the main analysis included only fracture data extracted at the longest timepoint of the trial, the subgroup analysis separately analyzed studies that reported fracture data at each year of treatment. Overall, results did not differ statistically from the main analysis by treatment year. One year of treatment included 17 studies (86, 94, 117, 120-122, 125, 132-138, 140, 143, 144), two years included 19 trials (80, 84, 86, 95, 117, 120, 122, 124, 131, 133, 134, 136, 137, 139, 141, 142, 144, 145, 147), three years treatment included 11 studies (86, 90, 117, 125, 133, 136, 138, 139, 144-146), four years treatment included three studies (85, 136, 148), and five years of treatment had the fewest included studies at two trials (87, 144).

Across the main analysis and all treatment durations, five interventions were consistently superior to placebo in significantly reducing vertebral fractures: alendronate 10 mg/day (42% to 65% reduction in odds), risedronate 5 mg/day (43% to 63% reduction in odds), etidronate 400 mg/day (56% to 88%

reduction in odds), zoledronic acid 5 mg/year (61% to 75% reduction) and minodronate 1 mg/day (81% to 92% reduction in odds). Three of these interventions had at least two studies providing direct evidence while zoledronic acid and minodronate were only assessed by one study each (125, 137).

Alendronate 5 mg/day was significantly better than placebo in the main analysis statistically, but not in the second and third year analyses. Alendronate combined with alfacalcidol or hormone replacement therapy did not show greater efficacy than placebo or any other intervention across all treatment durations. All doses of etidronate were superior to placebo across for each treatment duration except etidronate 200 mg/day in the first-year analysis (OR 0.73, 95% CrI: 0.23, 2.24).

Zoledronic acid was significantly better statistically compared to clodronate 800 mg/day and risedronate 5 mg/day in the main analysis. This was not observed in the first- and second-year analyses but re-appears in the third-year analysis. Zoledronic acid is superior to alendronate in the main analysis, but not among analyses with one, two or three years of treatment.

Minodronate was not better than any active treatment in the main analysis. However, in the one-year analysis, it was superior to alendronate 10 mg/day, etidronate 200 mg/day, oral ibandronate 2.5 mg/day, intravenous ibandronate 1 mg/month, risedronate 2.5 mg/day alone and combined with vitamin K. It was also significantly better than risedronate 2.5 mg/day in the second-year analysis. Minodronate was assessed directly in one study that provided data at one and two years of treatment (137). It was not included in networks for three, four or five years of treatment.

Among off-label treatments for postmenopausal osteoporosis, neridronate did not demonstrate better efficacy compared to placebo or other treatments, while tiludronate was worse than most approved bisphosphonates for reducing vertebral fractures. However, only one study each assessed the efficacy of neridronate and tiludronate.

Table 4.12: Staircase diagram for radiographic vertebral fractures (1 year)

PBO	**PBO**															
ALED10	**0.54 (0.37,0.85)**	**ALED10**														
ALED10+HRT	0.39 (0.07,1.93)	0.71 (0.14,3.37)	**ALED10 +HRT**													
ALED10 +RALD60	**0.11 (0.01,0.75)**	0.20 (0.02,1.31)	0.28 (0.02,2.51)	**ALED10 +RALD60**												
ETID200	0.73 (0.23,2.24)	1.35 (0.39,4.42)	1.82 (0.27,15.05)	6.66 (0.68,82.97)	**ETID200**											
ETID400	**0.12 (0.01,0.89)**	0.22 (0.02,1.73)	0.32 (0.01,4.33)	1.13 (0.04,25.15)	0.16 (0.01,1.78)	**ETID400**										
RISD2.5	**0.53 (0.34,0.85)**	0.98 (0.52,1.74)	1.36 (0.26,7.81)	4.72 (0.69,54.41)	0.72 (0.23,2.38)	4.36 (0.58,62.33)	**RISD2.5**									
RISD2.5 +VIKD45	0.82 (0.16,4.93)	1.50 (0.28,9.33)	2.17 (0.22,22.39)	7.41 (0.61,164.20)	1.16 (0.16,8.36)	6.87 (0.47,166.20)	1.57 (0.31,8.97)	**RISD2.5 +VIKD45**								
RISD5	**0.37 (0.22,0.59)**	0.68 (0.35,1.24)	0.94 (0.17,5.49)	3.31 (0.46,39.75)	0.51 (0.15,1.68)	3.04 (0.39,42.99)	0.69 (0.41,1.16)	0.45 (0.07,2.37)	**RISD5**							
IBAD2.5	0.61 (0.24,1.47)	1.13 (0.40,2.86)	1.56 (0.25,10.45)	5.50 (0.65,77.42)	0.83 (0.20,3.56)	5.06 (0.57,76.25)	1.15 (0.40,3.04)	0.74 (0.10,4.50)	1.65 (0.60,4.53)	**IBAD2.5**						
IBAM1	0.70 (0.33,1.46)	1.29 (0.53,2.89)	1.80 (0.31,10.89)	6.30 (0.85,71.55)	0.95 (0.26,3.56)	5.81 (0.65,84.92)	1.31 (0.70,2.44)	0.84 (0.13,4.62)	1.89 (0.84,4.19)	1.15 (0.36,3.71)	**IBAM1**					
ZOLY5	**0.39 (0.23,0.67)**	0.72 (0.36,1.39)	1.00 (0.18,5.89)	3.55 (0.47,40.69)	0.53 (0.15,1.89)	3.19 (0.40,46.83)	0.74 (0.36,1.46)	0.48 (0.07,2.67)	1.06 (0.52,2.19)	0.64 (0.23,1.84)	0.56 (0.22,1.40)	**ZOLY5**				
MIND1	**0.08 (0.01,0.41)**	**0.14 (0.01,0.78)**	0.19 (0.01,1.99)	0.69 (0.03,10.77)	**0.10 (0.01,0.75)**	0.60 (0.02,13.09)	**0.14 (0.01,0.83)**	**0.09 (0.003,0.96)**	0.21 (0.01,1.22)	**0.13 (0.01,0.80)**	**0.11 (0.01,0.72)**	0.19 (0.01,1.19)	**MIND1**			
CLOD800	0.37 (0.12,1.03)	0.68 (0.20,2.00)	0.94 (0.13,6.78)	3.49 (0.32,43.20)	0.51 (0.11,2.10)	3.03 (0.30,47.63)	0.69 (0.21,2.10)	0.44 (0.06,3.07)	1.00 (0.30,3.02)	0.60 (0.14,2.35)	0.53 (0.14,1.89)	0.94 (0.26,2.95)	4.93 (0.63,79.76)	**CLOD800**		
NERM25	0.25 (0.02,2.35)	0.46 (0.03,4.47)	0.62 (0.03,11.59)	2.24 (0.08,64.49)	0.35 (0.01,4.19)	1.98 (0.07,64.43)	0.47 (0.03,4.75)	0.30 (0.01,5.16)	0.68 (0.04,6.80)	0.40 (0.02,5.13)	0.35 (0.02,4.27)	0.64 (0.04,6.41)	3.34 (0.14,142.30)	0.68 (0.04,8.08)	**NERM25**	
TILM350	1.18 (0.68,2.09)	**2.18 (1.04,4.28)**	3.05 (0.55,17.97)	**10.70 (1.37,129.40)**	1.61 (0.47,5.80)	**9.73 (1.18,137.30)**	**2.24 (1.06,4.59)**	1.44 (0.21,7.85)	**3.22 (1.51,6.77)**	1.94 (0.68,5.77)	1.69 (0.66,4.51)	**3.01 (1.39,6.67)**	**15.57 (2.60,246.70)**	3.22 (1.00,11.06)	4.80 (0.45,81.43)	**TILM350**
TILM1400	1.03 (0.57,1.82)	1.88 (0.89,3.73)	2.60 (0.46,15.53)	**9.37 (1.20,108.50)**	1.40 (0.40,4.90)	**8.47 (1.03,121.30)**	1.92 (0.91,4.07)	1.25 (0.18,6.99)	**2.78 (1.31,5.95)**	1.67 (0.59,4.93)	1.46 (0.57,3.95)	**2.62 (1.17,5.67)**	**13.65 (2.29,212.90)**	2.79 (0.88,9.63)	4.13 (0.39,69.94)	0.86 (0.48,1.53)

Green cells with bolded black font indicate significant preventive effect or lower odds of adverse event, red cells with white bolded font indicate significant harmful effect. PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, RALD60=raloxifene 60 mg/day, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM1=ibandronate 1 mg/month, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, NERM25=neridronate 25 mg/month, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Table 4.13: Staircase diagram for radiographic vertebral fractures (2 years)

PBO	**PBO**															
ALED5	0.56 (0.27,1.14)	**ALED5**														
ALED5 +ALFD1	0.51 (0.19,1.35)	0.91 (0.47,1.78)	**ALED5 +ALFD1**													
ALED10	**0.35 (0.18,0.64)**	0.62 (0.24,1.59)	0.68 (0.21,2.14)	**ALED10**												
ALED10 +HRT	0.85 (0.10,8.02)	1.52 (0.17,16.39)	1.65 (0.17,19.81)	2.41 (0.28,24.57)	**ALED10 +HRT**											
ETID200	**0.23 (0.08,0.53)**	0.39 (0.12,1.24)	0.43 (0.11,1.57)	0.64 (0.19,1.85)	0.26 (0.02,2.55)	**ETID200**										
ETID400	**0.34 (0.15,0.72)**	0.61 (0.20,1.73)	0.66 (0.18,2.21)	0.97 (0.34,2.60)	0.39 (0.04,3.86)	1.51 (0.46,5.54)	**ETID400**									
ETID400 +PHOD2	**0.23 (0.04,0.86)**	0.41 (0.06,1.85)	0.46 (0.06,2.30)	0.66 (0.11,2.85)	0.27 (0.02,3.22)	1.03 (0.16,5.62)	0.70 (0.13,2.71)	**ETID400 +PHOD2**								
RISD2.5	0.76 (0.42,1.39)	1.35 (0.55,3.48)	1.48 (0.49,4.65)	2.16 (0.95,5.50)	0.90 (0.09,8.10)	**3.36 (1.20,11.35)**	2.25 (0.85,6.33)	3.27 (0.77,20.81)	**RISD2.5**							
RISD5	**0.51 (0.33,0.82)**	0.92 (0.40,2.19)	1.01 (0.35,2.97)	1.47 (0.71,3.37)	0.61 (0.06,5.44)	2.29 (0.88,7.41)	1.52 (0.64,3.95)	2.22 (0.57,13.60)	0.68 (0.37,1.27)	**RISD5**						
IBAD2.5	0.52 (0.25,1.09)	0.92 (0.34,2.63)	1.01 (0.30,3.41)	1.48 (0.57,4.02)	0.61 (0.06,5.93)	2.30 (0.75,8.20)	1.53 (0.54,4.69)	2.23 (0.51,14.58)	0.68 (0.26,1.73)	1.01 (0.41,2.32)	**IBAD2.5**					
IBAM1	0.44 (0.20,1.04)	0.78 (0.27,2.43)	0.86 (0.24,3.15)	1.25 (0.47,3.78)	0.52 (0.05,5.21)	1.96 (0.60,7.75)	1.30 (0.42,4.46)	1.91 (0.41,13.27)	0.58 (0.23,1.50)	0.85 (0.42,1.76)	0.85 (0.28,2.69)	**IBAM1**				
ZOLY5	0.57 (0.17,1.75)	1.02 (0.25,3.96)	1.12 (0.23,4.92)	1.64 (0.42,6.12)	0.67 (0.05,7.49)	2.53 (0.58,12.20)	1.69 (0.40,6.95)	2.46 (0.43,20.02)	0.74 (0.19,2.69)	1.12 (0.30,3.67)	1.10 (0.27,4.28)	1.31 (0.29,5.05)	**ZOLY5**			
MIND1	**0.19 (0.05,0.60)**	0.33 (0.07,1.33)	0.36 (0.07,1.69)	0.53 (0.12,2.02)	0.22 (0.02,2.36)	0.84 (0.16,4.00)	0.54 (0.12,2.34)	0.81 (0.12,6.16)	**0.25 (0.05,0.89)**	0.36 (0.08,1.25)	0.36 (0.08,1.43)	0.42 (0.08,1.74)	0.32 (0.06,1.76)	**MIND1**		
TILM350	1.17 (0.61,2.20)	2.08 (0.81,5.44)	2.29 (0.71,7.13)	**3.33 (1.38,8.37)**	1.39 (0.13,12.57)	**5.22 (1.82,17.45)**	**3.45 (1.32,9.74)**	**5.01 (1.20,33.16)**	1.54 (0.62,3.60)	**2.28 (1.01,4.75)**	2.27 (0.85,5.90)	2.67 (0.90,7.40)	2.04 (0.56,8.07)	**6.27 (1.62,29.08)**	**TILM350**	
TILM1400	0.96 (0.49,1.82)	1.71 (0.65,4.49)	1.87 (0.58,5.91)	**2.72 (1.13,6.87)**	1.14 (0.11,10.52)	**4.28 (1.47,14.47)**	**2.83 (1.07,8.02)**	4.11 (0.99,26.30)	1.26 (0.50,2.96)	1.87 (0.81,3.96)	1.85 (0.69,4.85)	2.18 (0.73,6.03)	1.67 (0.45,6.60)	**5.11 (1.34,23.79)**	0.82 (0.43,1.55)	**TILM1400**

Green cells with bolded black font indicate significant preventive effect or lower odds of adverse event, red cells with white bolded font indicate significant harmful effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone placement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM1=ibandronate 1 mg/month, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Table 4.14: Staircase diagram for radiographic vertebral fractures (3 years)

PBO	**PBO**								
ALED5	0.46 (0.15,1.20)	**ALED5**							
ALED10	**0.48 (0.29,0.74)**	1.03 (0.38,3.10)	**ALED10**						
ETID400	**0.18 (0.05,0.57)**	0.39 (0.07,2.02)	0.38 (0.09,1.31)	**ETID400**					
RISD5	**0.57 (0.37,0.84)**	1.23 (0.43,3.89)	1.19 (0.65,2.24)	3.12 (0.93,13.13)	**RISD5**				
IBAD2.5	**0.48 (0.26,0.88)**	1.05 (0.34,3.67)	1.02 (0.49,2.22)	2.66 (0.72,12.17)	0.86 (0.41,1.78)	**IBAD2.5**			
ZOLY5	**0.25 (0.15,0.41)**	0.54 (0.18,1.75)	0.52 (0.27,1.06)	1.35 (0.39,6.01)	**0.44 (0.23,0.84)**	0.51 (0.23,1.13)	**ZOLY5**		
CLOD800	0.63 (0.33,1.27)	1.38 (0.43,4.90)	1.32 (0.62,3.16)	3.46 (0.96,16.09)	1.11 (0.53,2.52)	1.28 (0.56,3.34)	**2.53 (1.14,6.00)**	**CLOD800**	
TILM350	1.11 (0.65,1.88)	2.40 (0.80,8.03)	**2.33 (1.17,4.81)**	**6.09 (1.76,26.92)**	**1.97 (1.01,3.81)**	**2.28 (1.05,5.10)**	**4.51 (2.15,9.27)**	1.78 (0.73,3.90)	**TILM350**
TILM1400	1.02 (0.60,1.73)	2.22 (0.73,7.32)	**2.15 (1.08,4.39)**	**5.55 (1.59,24.66)**	1.80 (0.93,3.47)	2.10 (0.96,4.73)	**4.13 (1.95,8.55)**	1.63 (0.66,3.64)	0.92 (0.54,1.55)	**TILM1400**

Green cells with bolded black font indicate significant preventive effect, red cells with white bolded font indicate significant harmful effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, ZOLY5=zoledronic acid 5 mg/year, CLOD800=clodronate 800 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Table 4.15: Staircase diagram for radiographic vertebral fractures (4 years)

PBO	**PBO**			
ALED10	0.54 (0.24,1.27)	**ALED10**		
ETID400	0.40 (0.12,1.22)	0.73 (0.17,2.83)	**ETID400**	
ETID400 +HRT	**0.11 (0.01,0.84)**	0.20 (0.01,1.76)	0.27 (0.01,2.36)	**ETID400 +HRT**

Green cell with bolded black font indicates significant preventive effect.
PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week,
ETID400=etidronate 400 mg/day, HRT=hormone replacement therapy.

Table 4.16: Staircase diagram for radiographic vertebral fractures (5 years)

PBO	**PBO**		
ALED10	0.85 (0.32,2.33)	**ALED10**	
RISD5	0.48 (0.18,1.28)	0.56 (0.14,2.28)	**RISD5**

PBO=placebo, ALED10=alendronate 10 mg/day or
70 mg/week, RISD5=risedronate 5 mg/day,
35 mg/week or 150 mg/month.

4.3.4.3 SENSITIVITY ANALYSES

Baseline denominators

Sensitivity analysis using baseline denominators did not differ significantly from the main analysis where analysis denominators were used. One change occurred where risedronate 2.5 mg/day was not statistically significantly better than placebo in the main analysis (OR 0.75, 95% CrI: 0.29, 1.55) but was significantly more effective in the sensitivity analysis (OR 0.43, 95% CrI: 0.19, 0.93). The shift in statistical significance is likely due to a protocol change in a study that assessed risedronate doses 2.5 mg and 5 mg/day compared to placebo (124). A protocol amendment based on newly published efficacy and safety results caused 76 patients in the 2.5 mg/day arm to be withdrawn before the end of the trial. Since these participants were withdrawn from the study, the publication only reported end-of-trial results for radiographic vertebral fracture incidence in the 60 participants

with available radiographs who remained in the study (8/60, 13%). In the sensitivity analysis, the same event number remained the same but the denominator was taken as the number randomized (8/184, 4%), thus the efficacy of risedronate 2.5 mg/day appeared to increase. However, when using the randomized denominator, we are assuming none of the withdrawn 76 participants sustained radiographic vertebral fractures for the remaining duration of the trial.

Low risk of bias

A total of 13 studies (total 15583 participants) were judged low risk of bias in the domain of incomplete efficacy outcome data (85-87, 90, 121, 122, 125, 132, 134, 140, 143, 147, 148). Criteria for low risk of bias in the domain included greater than 80% followup at the end of the trial, and similar rates and reasons for withdrawal in all arms. Alendronate 10 mg/day had the most number of direct comparisons (4 studies), followed by risedronate 2.5 mg/day (3 studies). There were a few differences from the main analysis, although most results were similar. Alendronate 10 mg/day plus raloxifene 60 mg/day was not significantly better than placebo for reducing vertebral fractures in the main analysis but became more effective than placebo in the sensitivity analysis (OR 0.12, 95% CrI: 0.01, 0.87). Etidronate 200 mg/day, 400 mg/day, and risedronate 5 mg/day were previously better than placebo but became non-significant in the sensitivity analysis. This may indicate these effect estimates are not robust when we examine studies with higher quality in efficacy outcome reporting.

Approved bisphosphonates

Of the 32 studies reporting radiographic vertebral fractures, 27 assessed one of the five bisphosphonates that is approved in most countries for postmenopausal osteoporosis (total 23895 participants). The five studies excluded from the sensitivity analysis examined neridronate (132), minodronate (137), tiludronate (120) and clodronate (138, 146). The sensitivity analysis included studies published from 1990 to 2014, with study durations from 48 weeks to four years. The resulting effect estimates did not differ significantly from the main analysis.

Fracture as efficacy outcome

A total of 15 studies listed fracture incidence as an efficacy outcome of interest (total 22287 participants) (84-86, 90, 94, 117, 120, 125, 131, 133, 137, 138, 141, 144, 145). Publication years ranged from 1995 to 2014, and treatment duration from one to five years. Except for two studies with sample sizes under 50, most studies included more than 300 people. Etidronate 200 mg/day was previously assessed by three studies in the main analysis and was only better than placebo. It showed no significant reduction in radiographic vertebral fracture compared to other treatments. However, in the sensitivity analysis, it became significantly better than alendronate 5 mg/day, alendronate 5 mg/day plus alfalcalcidol, alendronate 10 mg/day, risedronate 5 mg/day, ibandronate 2.5 mg/day, zoledronic acid 5 mg/year, clodronate 800 mg/day, and all doses of tiludronate. The resulting credible intervals were all relatively wide. A possible reason for the discrepancy may be the number of studies assessing etidronate 200 mg/day (three in the main analysis; one in the sensitivity). The only study included in the sensitivity (145) showed more women had fractures in the placebo arm (11/20, 55%) than the etidronate arm (1/20, 5%). The drastic difference in fracture incidence may have been represented in the effect estimates, and may provide an inflated efficacy of etidronate. It is also possible etidronate 200 mg/day attains higher efficacy in larger trials designed to assess fractures; however, the broad credible interval indicates there is low precision around the effect estimates.

Change in criteria for primary and secondary prevention

All studies were re-classified using 2.5 SD instead of 2 SD for the BMD and T-score thresholds into primary and secondary prevention studies. No study changed in classification compared to the subgroup analysis when 2 SD was used instead of 2.5 SD. This indicates that the shift in thresholds did not significantly impact study classification.

4.3.5 CLINICAL VERTEBRAL FRACTURES

4.3.5.1 MAIN ANALYSIS

Eleven studies were included in the network for clinical vertebral fractures (total 15596 participants), of which two were classified as primary prevention studies and nine were secondary prevention trials (82, 86, 87, 91, 95, 117, 125, 130, 149-151). Publication years ranged from 1996 to 2008 and study duration from two to five years. The most common comparison was alendronate 10 mg/day to placebo (4 studies). Only alendronate 10 mg/day (OR 0.44, 95% CrI: 0.26, 0.72) and zoledronic acid 5 mg/year (OR 0.22, 95% CrI: 0.10, 0.44) were significantly superior to placebo statistically in terms of preventing clinical vertebral fractures. These two treatments were not significantly better than each other, although patients taking zoledronic acid are associated with a 50% reduction in odds of clinical vertebral fracture compared to alendronate (OR 0.50, 95% CrI: 0.20, 1.20). Zoledronic acid showed significantly greater efficacy than risedronate 2.5 mg/day (OR 0.21, 95% CrI: 0.06, 0.71) and 5 mg/day (OR 0.23, 95% CrI: 0.06, 0.86) for preventing clinical vertebral fractures. The only included combination treatment (alendronate 10 mg/day and HRT) did not show greater efficacy than placebo or other treatments.

Figure 4.6: Network diagram for clinical vertebral fractures

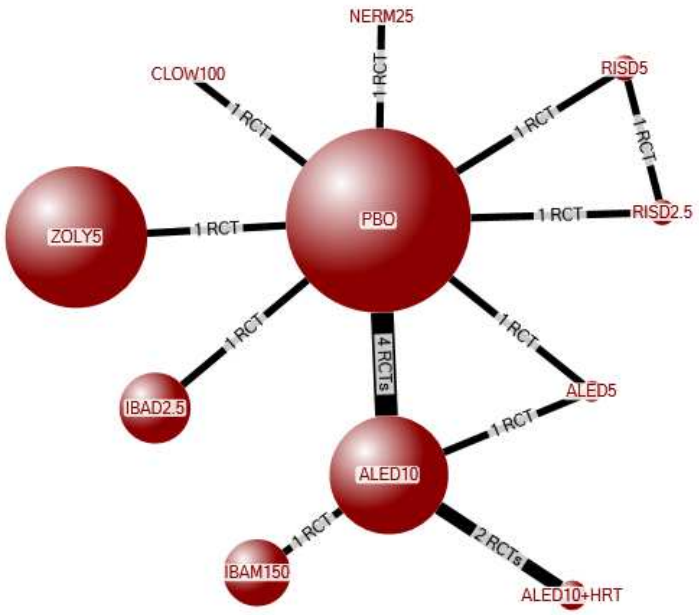


Table 4.17: Staircase diagram for clinical vertebral fractures

PBO	**PBO**										
ALED5	0.97 (0.07,10.69)	**ALED5**									
ALED10	**0.44 (0.26,0.72)**	0.44 (0.04,6.29)	**ALED10**								
ALED10 +HRT	0.98 (0.19,5.24)	1.01 (0.05,18.19)	2.21 (0.44,11.72)	**ALED10 +HRT**							
RISD2.5	1.05 (0.39,3.06)	1.07 (0.08,19.12)	2.38 (0.81,7.98)	1.07 (0.15,7.05)	**RISD2.5**						
RISD5	0.93 (0.32,2.78)	0.95 (0.08,17.27)	2.12 (0.66,7.58)	0.96 (0.12,6.74)	0.89 (0.31,2.47)	**RISD5**					
IBAD2.5	0.52 (0.24,1.08)	0.53 (0.04,8.21)	1.18 (0.48,2.93)	0.53 (0.08,3.03)	0.49 (0.13,1.73)	0.55 (0.15,2.10)	**IBAD2.5**				
IBAM150	0.42 (0.10,1.66)	0.42 (0.02,7.75)	0.95 (0.25,3.54)	0.43 (0.05,3.45)	0.39 (0.07,2.18)	0.45 (0.07,2.68)	0.81 (0.17,3.92)	**IBAM150**			
ZOLY5	**0.22 (0.10,0.44)**	0.23 (0.02,3.50)	0.50 (0.20,1.20)	0.22 (0.04,1.30)	**0.21 (0.06,0.71)**	**0.23 (0.06,0.86)**	0.42 (0.15,1.18)	0.52 (0.11,2.55)	**ZOLY5**		
CLOW100	0.80 (0.03,19.55)	0.76 (0.02,48.38)	1.81 (0.07,43.89)	0.78 (0.02,24.26)	0.76 (0.02,21.10)	0.87 (0.02,23.18)	1.53 (0.05,38.62)	1.94 (0.05,53.55)	3.69 (0.13,96.02)	**CLOW100**	
NERM25	0.41 (0.03,4.08)	0.42 (0.01,14.99)	0.94 (0.06,9.88)	0.43 (0.01,6.87)	0.39 (0.02,4.58)	0.43 (0.02,5.49)	0.79 (0.05,8.94)	0.98 (0.05,14.67)	1.85 (0.11,21.77)	0.50 (0.01,28.85)	**NERM25**

Green cells with bolded black font indicate significant preventive effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM150=ibandronate 150 mg/month, ZOLY5=zoledronic acid 5 mg/year, CLOW100=clodronate 100 mg/week, NERM25=neridronate 25 mg/month.

4.3.5.2 SUBGROUP ANALYSES

Primary and secondary prevention

None of the four bisphosphonate treatments included in the two primary prevention studies (total 647 participants) showed greater efficacy than placebo or any other intervention in reducing clinical vertebral fractures (82, 150). In the subgroup analysis including nine secondary prevention studies (total 14948 participants), no significant changes were observed in the odds ratios compared to the main analysis.

Figure 4.7: Network diagram for clinical vertebral fractures (primary prevention)

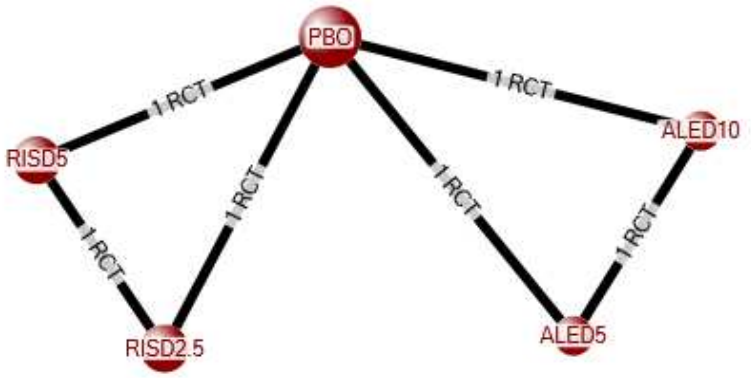


Table 4.18: Staircase diagram for clinical vertebral fractures (primary prevention)

PBO	**PBO**				
ALED5	0.92 (0.06,13.07)	**ALED5**			
ALED10	0.16 (0.001,4.66)	0.18 (0.001,6.65)	**ALED10**		
RISD2.5	1.06 (0.32,3.54)	1.17 (0.06,24.45)	6.81 (0.18,1139)	**RISD2.5**	
RISD5	0.95 (0.29,3.24)	1.05 (0.06,21.72)	5.98 (0.16,1030)	0.89 (0.27,3.05)	**RISD5**

PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month.

Figure 4.8: Staircase diagram for clinical vertebral fractures (secondary prevention)

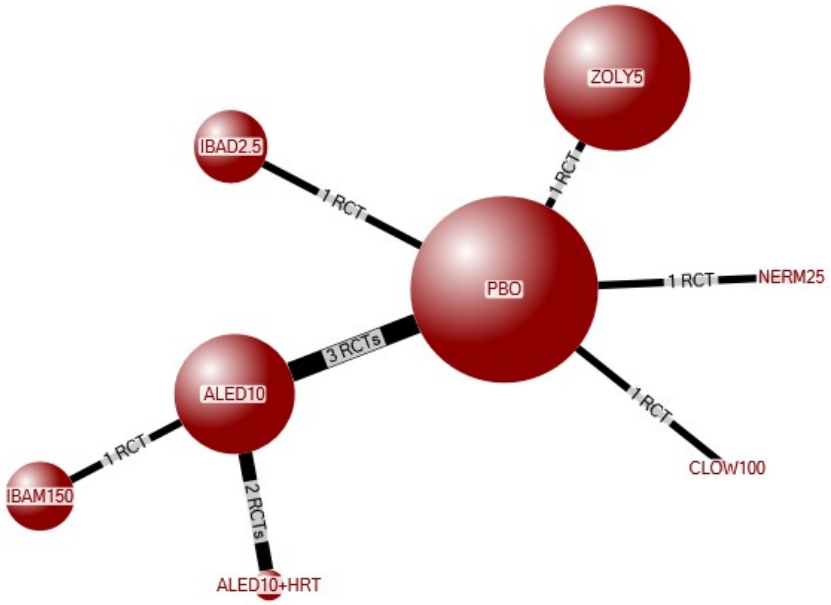


Table 4.19: Staircase diagram for clinical vertebral fractures (secondary prevention)

PBO	**PBO**							
ALED10	**0.44 (0.26,0.74)**	**ALED10**						
ALED10 +HRT	0.94 (0.19,5.11)	2.15 (0.46,11.78)	**ALED10 +HRT**					
IBAD2.5	0.52 (0.25,1.09)	1.19 (0.48,2.99)	0.55 (0.09,3.17)	**IBAD2.5**				
IBAM150	0.41 (0.09,1.76)	0.94 (0.23,3.71)	0.43 (0.05,3.50)	0.78 (0.15,4.06)	**IBAM150**			
ZOLY5	**0.22 (0.11,0.45)**	0.50 (0.20,1.23)	0.23 (0.04,1.29)	0.42 (0.15,1.19)	0.53 (0.11,2.81)	**ZOLY5**		
CLOW100	0.83 (0.03,16.47)	1.92 (0.07,41.02)	0.87 (0.02,26.83)	1.61 (0.05,35.16)	2.06 (0.05,55.63)	3.81 (0.12,82.54)	**CLOW100**	
NERM25	0.42 (0.02,5.23)	0.96 (0.04,12.54)	0.43 (0.01,8.43)	0.80 (0.03,11.03)	1.01 (0.03,18.09)	1.90 (0.07,26.44)	0.48 (0.01,33.01)	**NERM25**

Green cells with bolded black font indicate significant preventive effect. PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, IBAD2.5=ibandronate 2.5 mg/day, IBAM150=ibandronate 150 mg/month, ZOLY5=zoledronic acid 5 mg/year, CLOW100=clodronate 100 mg/week, NERM25=neridronate 25 mg/month.

Prior bisphosphonate experience

An NMA could not be conducted for studies among bisphosphonate-experienced participants because only the FLEX trial included participants who had at least three years of alendronate experience. Descriptively, the event rate of clinical vertebral fractures was lower in the alendronate 10 mg/day arm (16/662, 2.4%) compared to the placebo (23/437, 5.3%). A total of four studies (total 4226 participants) selectively enrolled bisphosphonate-naïve, postmenopausal women (82, 86, 117, 151). Ranging from 1996 to 2004, three are three-year studies and one is a two-year study. Only alendronate 10 mg/day was significant and only when compared to placebo. Zoledronic acid was not included. Among those without prior bisphosphonate treatment, patients receiving alendronate has a 59% reduction in odds of fracture compared to those receiving placebo (OR 0.41, 95% CrI: 0.17, 0.95). The reduction is 56% among postmenopausal women in the main analysis with any level of treatment experience (OR 0.44, 95% CrI: 0.26, 0.72).

Figure 4.9: Network diagram for clinical vertebral fractures (bisphosphonate-naïve)

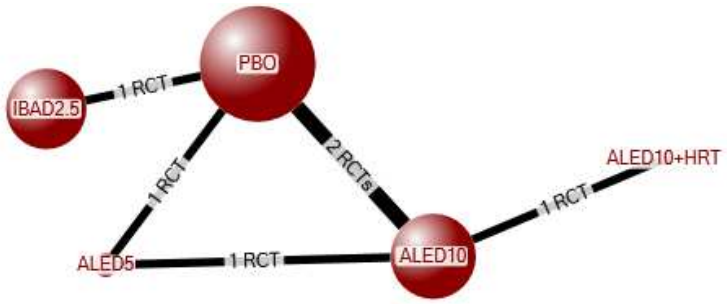


Table 4.20: Staircase diagram for clinical vertebral fractures (bisphosphonate-naïve)

PBO	**PBO**				
ALED5	0.94 (0.04,10.02)	**ALED5**			
ALED10	**0.41 (0.17,0.95)**	0.44 (0.04,10.20)	**ALED10**		
ALED10 +HRT	0.94 (0.05,50.10)	1.03 (0.02,104.80)	2.28 (0.13,110.10)	**ALED10+HRT**	
IBAD2.5	0.52 (0.20,1.31)	0.55 (0.04,12.84)	1.24 (0.37,4.57)	0.54 (0.01,12.28)	**IBAD2.5**

Green cell with bolded black font indicates significant preventive effect.PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, IBAD2.5 =ibandronate 2.5 mg/day.

Treatment durations

Subgroup analyses could not be conducted due to insufficient data for studies with one year of treatment (one study), four years of treatment (zero studies), and five years of treatment (one study). Networks were conducted only for two years of treatment which included 5 studies (95, 130, 149-151) and three years of treatment which included 4 studies (82, 86, 117, 125). In the main analysis, alendronate 10 mg/day and zoledronic acid 5 mg/day were more effective than placebo at reducing clinical vertebral fractures, however this was only seen in the third-year analysis. This indicates the observed efficacy of zoledronic acid and alendronate in the main analysis are likely centered around three-year data. Zoledronic acid was more effective than both risedronate 2.5 mg/day and 5 mg/day at preventing clinical vertebral fractures based on the main analysis, however, there was not enough data to examine these comparisons in any of the treatment duration subgroups.

Table 4.21: Staircase diagram for clinical vertebral fractures (2 years)

PBO	**PBO**						
ALED10	0.47 (0.03,8.48)	**ALED10**					
ALED10 +HRT	1.09 (0.14,16.52)	2.35 (0.38,22.19)	**ALED10 +HRT**				
RISD2.5	1.07 (0.34,3.43)	2.32 (0.10,42.86)	0.98 (0.05,10.93)	**RISD2.5**			
RISD5	0.95 (0.29,3.14)	2.04 (0.09,39.12)	0.86 (0.05,9.73)	0.89 (0.27,2.88)	**RISD5**		
CLOW100	0.74 (0.03,17.98)	1.52 (0.02,95.64)	0.64 (0.01,28.76)	0.69 (0.02,21.02)	0.78 (0.02,23.99)	**CLOW100**	
NERM25	0.44 (0.02,5.12)	0.89 (0.01,38.43)	0.37 (0.01,10.23)	0.40 (0.01,6.15)	0.45 (0.02,7.11)	0.57 (0.01,36.78)	**NERM25**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, RISD2.5 =risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, CLOW100=clodronate 100 mg/week, NERM25=neridronate 25 mg/month.

Table 4.22: Staircase diagram for clinical vertebral fractures (3 years)

PBO	**PBO**				
ALED5	0.91 (0.06,10.89)	**ALED5**			
ALED10	**0.43 (0.17,0.94)**	0.46 (0.04,7.03)	**ALED10**		
IBAD2.5	0.52 (0.21,1.32)	0.57 (0.04,9.96)	1.23 (0.37,4.63)	**IBAD2.5**	
ZOLY5	**0.22 (0.09,0.56)**	0.24 (0.02,4.14)	0.51 (0.16,1.96)	0.42 (0.12,1.55)	**ZOLY5**

Green cells with bolded black font indicate significant preventive effect.PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10 =alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, IBAD2.5 =ibandronate 2.5 mg/day, ZOLY5=zoledronic acid 5 mg/year.

4.3.5.3 SENSITIVITY ANALYSES

Baseline denominators

There were no substantial changes in any of the effect estimates when the numbers of randomized participants were used instead of participants included in analyses. This indicates that effect estimates were not affected by the use of baseline or analysis denominators.

Low risk of bias

A total of four studies (12514 participants) met the criteria for low risk of bias due to incomplete efficacy outcome data (86, 87, 91, 125). Publication of the studies ranged from 1996 to 2008 and durations from 1 to 5 years. Two studies compared placebo to alendronate 10 mg/day, one compared placebo to zoledronic acid 5 mg/year, and one study compared alendronate 10 mg/day to ibandronate 150 mg/month. Due to a small number of included studies, most comparisons in the main analysis were missing from the sensitivity analysis. However, alendronate 10 mg/day and zoledronic acid 5 mg/year remained significantly better than placebo (OR 0.44, 95% CrI: 0.25, 0.77, and OR 0.22, 95% CrI: 0.10, 0.48), with odds ratios identical to those found in the main analysis. This suggests estimates in the main analysis are robust even when only higher quality studies are assessed.

Approved bisphosphonates

Nine studies were included in the sensitivity analysis (total 15455 participants), published from 1996 to 2008, ranging from 1 to 5 years, and comprising of 6 two-arm studies and 3 three-arm studies (82, 86, 87, 91, 95, 117, 125, 150, 151). Six trials examined alendronate 10 mg/day. The results are identical to the main analysis. Alendronate 10 mg/day and zoledronic acid 5 mg/year are significantly better than placebo in the both the sensitivity and the main analysis. Zoledronic acid remains significantly better than risedronate 2.5 mg and 5 mg/day. This indicates removal of unapproved bisphosphonates does not impact effect estimates of the main analysis.

Fracture as efficacy outcome

Three studies listed fracture incidence as an efficacy outcome (total 11634 participants): FIT (Vertebral Fracture Study) assessing placebo and alendronate 10 mg/day, HORIZON comparing placebo to zoledronic acid 5 mg/year, and a three-year, trial comparing placebo to ibandronate 2.5 mg/day (117). The studies have sample sizes ranging from 1952 to 7736 participants. Zoledronic acid 5 mg/year remains more effective than placebo at preventing clinical vertebral fractures (OR 0.22, 95% CrI: 0.08, 0.62). No other significant comparisons were found in the network. Alendronate 10 mg/day is no longer significantly better than placebo in the sensitivity analysis (OR 0.43, 95% CrI: 0.16, 1.20) due to a widening of the credible interval compared to the main analysis (OR 0.44, 95% CrI: 0.26, 0.72). These results indicate while the effect estimate of zoledronic acid 5 mg/year in the main analysis is relatively robust, the estimate for alendronate and placebo varies depending on the included studies. The significant result found in the main analysis is likely based on results of the three additional studies examining alendronate and placebo excluded from the sensitivity analysis.

Change in criteria for primary and secondary prevention

After the re-classification using 2.5 instead of 2 in both BMD and T-score thresholds, none of the included studies changed in prevention trial type. This indicates that the shift in thresholds did not significantly impact the classification of studies into primary or secondary prevention.

4.3.6 NON-VERTEBRAL FRACTURES

4.3.6.1 MAIN ANALYSIS

Of the 43 studies included in the network investigating the odds of a non-vertebral fracture (total 45779 participants), 9 were primary prevention studies and 34 were secondary prevention studies (80, 82, 84-87, 90, 91, 95, 96, 117, 120, 121, 124, 125, 128, 133, 134, 136, 137, 141, 144, 146-148, 150-167). Only alendronate 10 mg/day had a significant 22% reduction in odds of sustaining non-vertebral fractures compared to placebo (OR 0.78, 95% CrI: 0.60, 0.98). No other treatment showed significantly greater efficacy compared to placebo or other interventions.

Inconsistency was detected within the placebo and etidronate 400 mg/day arms of the study by Watts et al. (1990). Potential causes of inconsistency may be the difference in race of included participants and shorter calcium supplementation period compared to other studies within the same closed loop (Appendix 8). No substantial differences were found in a sensitivity analysis excluding the study (Appendix 8).

Figure 4.10: Network diagram for non-vertebral fractures

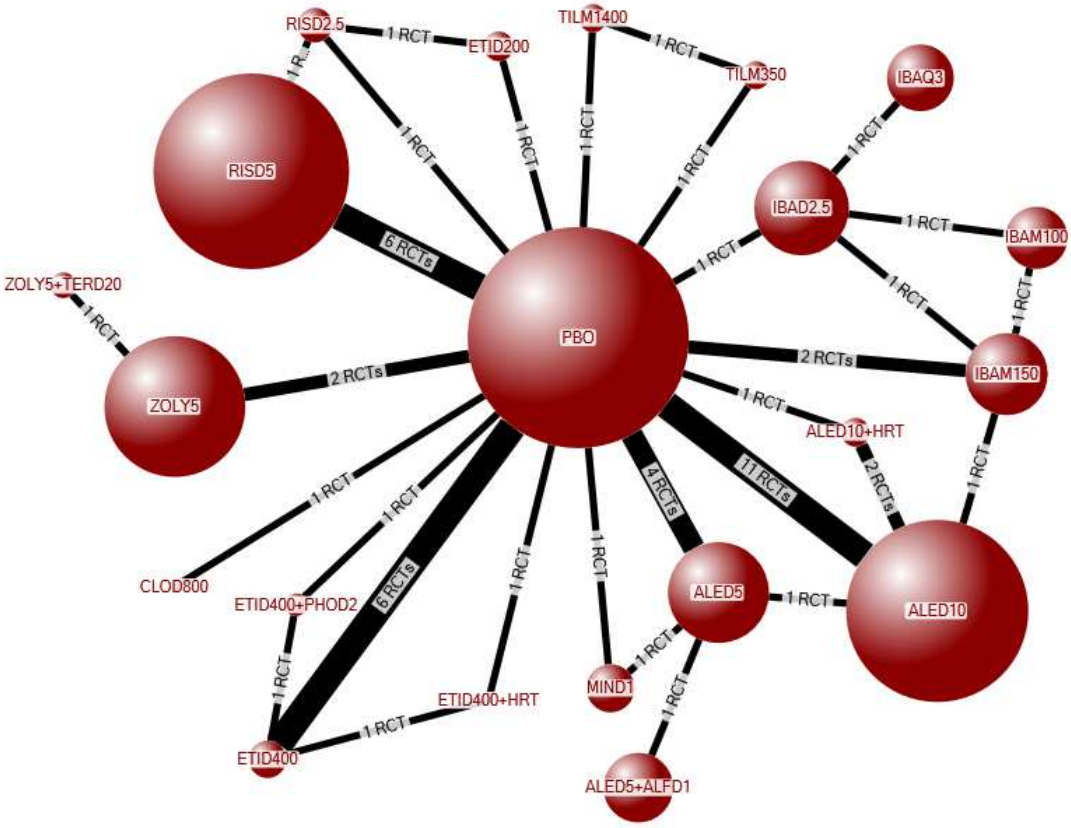


Table 4.23: Staircase diagram for non-vertebral fractures

PBO	**PBO**																		
ALED5	0.86 (0.54,1.37)	**ALED5**																	
ALED5 +ALFD1	0.57 (0.20,1.49)	0.66 (0.26,1.57)	**ALED5 +ALFD1**																
ALED10	**0.78 (0.60,0.98)**	0.90 (0.53,1.50)	1.37 (0.50,3.98)	**ALED10**															
ALED10 +HRT	0.45 (0.14,1.39)	0.52 (0.15,1.80)	0.79 (0.18,3.80)	0.58 (0.18,1.78)	**ALED10 +HRT**														
ETID200	0.27 (0.05,1.11)	0.32 (0.06,1.38)	0.48 (0.07,2.84)	0.35 (0.07,1.50)	0.61 (0.08,3.70)	**ETID200**													
ETID400	0.86 (0.49,1.50)	0.99 (0.47,2.04)	1.51 (0.49,4.87)	1.10 (0.60,2.01)	1.89 (0.55,6.65)	3.12 (0.69,17.36)	**ETID400**												
ETID400 +HRT	0.62 (0.04,6.33)	0.72 (0.04,7.78)	1.09 (0.06,14.06)	0.81 (0.05,8.24)	1.37 (0.07,19.15)	2.28 (0.10,38.77)	0.74 (0.05,7.15)	**ETID400 +HRT**											
ETID400 +PHOD2	0.66 (0.29,1.48)	0.77 (0.30,1.92)	1.17 (0.33,4.34)	0.85 (0.36,1.98)	1.47 (0.37,5.91)	2.43 (0.47,15.04)	0.78 (0.34,1.77)	1.03 (0.09,20.78)	**ETID400 +PHOD2**										
RISD2.5	0.46 (0.12,1.49)	0.53 (0.13,1.88)	0.79 (0.15,4.13)	0.59 (0.15,2.00)	1.01 (0.17,5.34)	1.65 (0.51,6.10)	0.54 (0.13,1.96)	0.72 (0.05,15.53)	0.68 (0.15,2.93)	**RISD2.5**									
RISD5	0.83 (0.58,1.11)	0.96 (0.54,1.66)	1.46 (0.50,4.24)	1.07 (0.71,1.53)	1.84 (0.57,6.00)	3.03 (0.71,16.17)	0.97 (0.51,1.83)	1.32 (0.13,23.86)	1.25 (0.52,2.99)	1.80 (0.54,6.84)	**RISD5**								
IBAD2.5	1.06 (0.63,1.74)	1.23 (0.61,2.42)	1.87 (0.62,5.92)	1.36 (0.79,2.35)	2.36 (0.69,8.15)	3.87 (0.87,21.61)	1.23 (0.60,2.65)	1.68 (0.16,29.85)	1.60 (0.61,4.18)	2.32 (0.63,9.64)	1.27 (0.73,2.37)	**IBAD2.5**							
IBAM100	1.00 (0.46,2.14)	1.17 (0.47,2.84)	1.75 (0.51,6.39)	1.28 (0.59,2.82)	2.21 (0.58,8.89)	3.69 (0.73,21.53)	1.18 (0.46,3.04)	1.60 (0.14,29.42)	1.52 (0.49,4.52)	2.22 (0.53,9.80)	1.20 (0.54,2.79)	0.94 (0.48,1.90)	**IBAM100**						
IBAM150	0.98 (0.53,1.83)	1.14 (0.53,2.45)	1.73 (0.55,5.87)	1.26 (0.68,2.38)	2.17 (0.62,8.21)	3.61 (0.77,19.73)	1.15 (0.50,2.67)	1.56 (0.14,27.34)	1.49 (0.53,4.11)	2.19 (0.57,9.07)	1.19 (0.61,2.42)	0.93 (0.50,1.73)	0.99 (0.50,1.93)	**IBAM150**					
IBAQ3	0.68 (0.27,1.62)	0.79 (0.28,2.08)	1.20 (0.31,4.56)	0.87 (0.35,2.15)	1.51 (0.35,6.27)	2.48 (0.46,15.64)	0.79 (0.28,2.33)	1.06 (0.09,20.58)	1.02 (0.30,3.43)	1.49 (0.33,7.11)	0.81 (0.32,2.11)	0.64 (0.30,1.33)	0.67 (0.24,1.85)	0.68 (0.26,1.80)	**IBAQ3**				
ZOLY5	0.70 (0.43,1.13)	0.81 (0.41,1.59)	1.24 (0.42,3.88)	0.90 (0.53,1.59)	1.57 (0.46,5.33)	2.59 (0.57,14.34)	0.82 (0.39,1.73)	1.12 (0.11,20.36)	1.05 (0.41,2.75)	1.55 (0.42,6.32)	0.84 (0.49,1.56)	0.66 (0.33,1.36)	0.70 (0.28,1.76)	0.71 (0.32,1.56)	1.04 (0.38,2.98)	**ZOLY5**			
ZOLY5 +TERD20	0.38 (0.08,1.53)	0.44 (0.09,1.90)	0.66 (0.11,3.90)	0.48 (0.10,2.04)	0.84 (0.12,4.95)	1.37 (0.17,12.48)	0.44 (0.09,2.01)	0.60 (0.03,14.54)	0.57 (0.10,2.90)	0.82 (0.12,5.68)	0.45 (0.10,1.94)	0.36 (0.07,1.58)	0.38 (0.07,1.86)	0.38 (0.07,1.75)	0.55 (0.10,3.02)	0.54 (0.13,1.98)	**ZOLY5 +TERD20**		
MIND1	0.61 (0.25,1.46)	0.71 (0.28,1.81)	1.08 (0.31,4.01)	0.79 (0.32,1.96)	1.36 (0.33,5.45)	2.25 (0.41,14.33)	0.71 (0.25,2.07)	0.98 (0.08,18.22)	0.92 (0.28,3.07)	1.34 (0.31,6.54)	0.74 (0.30,1.90)	0.58 (0.21,1.61)	0.61 (0.19,1.97)	0.62 (0.21,1.81)	0.90 (0.26,3.22)	0.87 (0.32,2.35)	1.66 (0.31,9.05)	**MIND1**	
CLOD800	0.62 (0.02,8.16)	0.72 (0.02,9.51)	1.10 (0.03,17.00)	0.80 (0.03,10.75)	1.37 (0.04,22.36)	2.17 (0.06,52.21)	0.73 (0.02,10.27)	1.02 (0.01,43.13)	0.93 (0.03,14.16)	1.31 (0.04,25.92)	0.75 (0.03,10.11)	0.58 (0.02,8.04)	0.61 (0.02,9.14)	0.63 (0.02,8.86)	0.90 (0.03,14.51)	0.88 (0.03,11.99)	1.64 (0.05,31.72)	1.02 (0.03,14.94)	**CLOD800**
TILM350	0.71 (0.29,1.65)	0.82 (0.30,2.14)	1.25 (0.33,4.70)	0.91 (0.36,2.22)	1.56 (0.38,6.37)	2.58 (0.48,16.33)	0.82 (0.29,2.38)	1.11 (0.10,22.91)	1.05 (0.32,3.64)	1.54 (0.36,7.32)	0.85 (0.34,2.19)	0.67 (0.24,1.80)	0.70 (0.22,2.25)	0.71 (0.24,2.11)	1.04 (0.30,3.72)	1.00 (0.37,2.72)	1.88 (0.36,10.54)	1.15 (0.33,3.85)	1.14 (0.08,36.83)	**TILM350**
TILM1400	0.48 (0.19,1.19)	0.56 (0.20,1.52)	0.85 (0.22,3.30)	0.62 (0.24,1.60)	1.07 (0.25,4.54)	1.75 (0.32,11.54)	0.57 (0.19,1.65)	0.76 (0.06,16.00)	0.72 (0.21,2.53)	1.06 (0.24,5.36)	0.58 (0.22,1.57)	0.45 (0.16,1.31)	0.48 (0.14,1.59)	0.49 (0.16,1.46)	0.71 (0.20,2.56)	0.68 (0.25,1.94)	1.29 (0.24,7.52)	0.79 (0.22,2.78)	0.78 (0.05,25.36)	0.69 (0.26,1.80)	**TILM1400**

Green cell with bolded black font indicates significant preventive effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year, TERD20=teriparatide 20 µg/day, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

4.3.6.2 SUBGROUP ANALYSES

Primary and secondary prevention

The network including nine primary prevention studies (total 6658 participants) found no significant differences in efficacy among any of the treatments (82, 85, 128, 150, 156, 158, 160, 163, 167). Unlike the main analysis, alendronate 10 mg/day was no longer more effective than placebo for reducing the odds of non-vertebral fracture (OR 0.87, 95% CrI: 0.49, 1.47). The network comprising of thirty-four secondary prevention studies (total 39121 participants) matched the main analysis findings where only alendronate 10 mg/day is significantly better than placebo at reducing non-vertebral fractures (OR 0.75, 95% CrI: 0.54, 0.99). The subgroup analysis shows a 25% reduction in likelihood of fracture among those receiving alendronate 10 mg/day compared to placebo, while the main analysis shows a 23% reduction (OR 0.78, 95% CrI: 0.60, 0.98).

Figure 4.11: Network diagram for non-vertebral fractures (primary prevention)

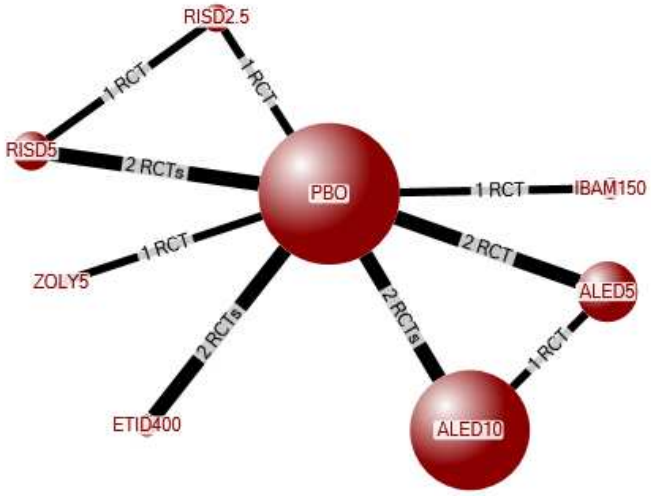


Table 4.24: Staircase diagram for non-vertebral fractures (primary prevention)

PBO	**PBO**							
ALED5	1.28 (0.59,2.59)	**ALED5**						
ALED10	0.87 (0.49,1.47)	0.68 (0.29,1.67)	**ALED10**					
ETID400	0.51 (0.14,1.69)	0.40 (0.09,1.67)	0.59 (0.15,2.19)	**ETID400**				
RISD2.5	0.41 (0.08,1.66)	0.33 (0.06,1.61)	0.48 (0.09,2.12)	0.81 (0.11,5.37)	**RISD2.5**			
RISD5	0.65 (0.20,2.03)	0.51 (0.13,2.01)	0.75 (0.21,2.65)	1.28 (0.24,7.11)	1.57 (0.35,8.30)	**RISD5**		
IBAM150	0.96 (0.11,8.04)	0.76 (0.08,7.31)	1.12 (0.12,9.98)	1.89 (0.16,23.22)	2.37 (0.17,34.69)	1.49 (0.12,17.04)	**IBAM150**	
ZOLY5	0.26 (0.01,2.39)	0.20 (0.01,2.15)	0.30 (0.01,2.97)	0.50 (0.02,6.84)	0.61 (0.02,9.45)	0.40 (0.02,5.08)	0.25 (0.007,6.67)	**ZOLY5**

PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAM150=ibandronate 150 mg/month, ZOLY5=zoledronic acid 5 mg/year.

Figure 4.12: Network diagram for non-vertebral fractures (secondary prevention)

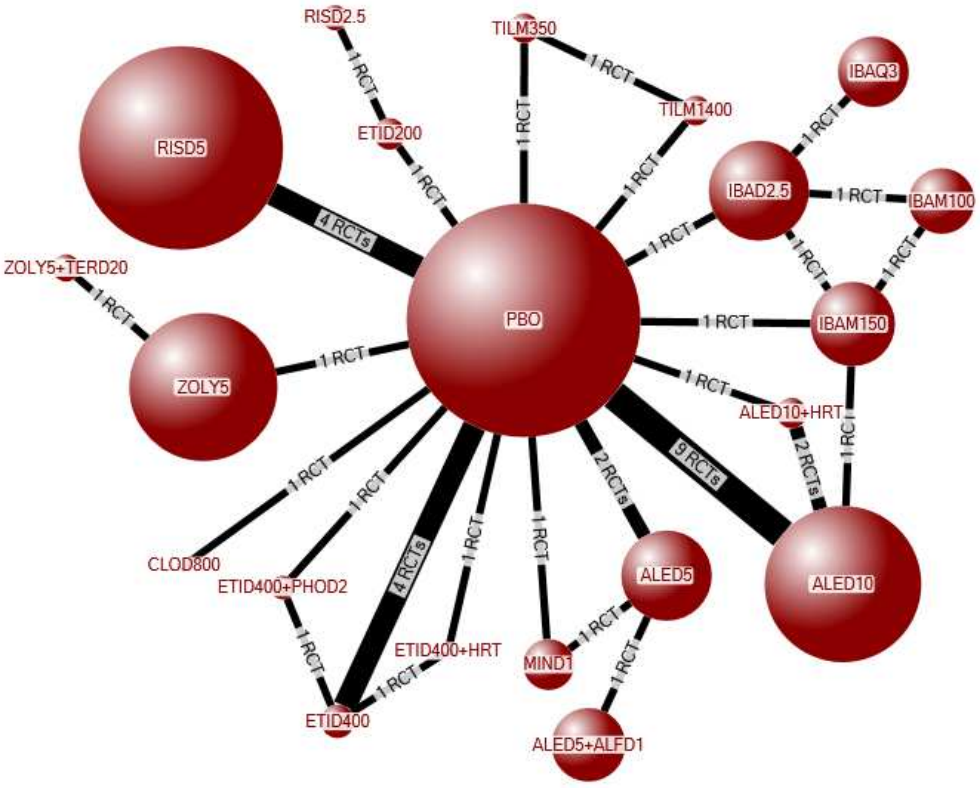


Table 4.25: Staircase diagram for non-vertebral fractures (secondary prevention)

PBO	**PBO**																				
ALED5	0.60 (0.31,1.16)	**ALED5**																			
ALED5 +ALFD1	0.39 (0.13,1.19)	0.65 (0.26,1.58)	**ALED5 +ALFD1**																		
ALED10	**0.75 (0.54,0.99)**	1.24 (0.60,2.58)	1.91 (0.60,6.10)	**ALED10**																	
ALED10+HRT	0.45 (0.13,1.42)	0.75 (0.19,2.90)	1.15 (0.21,5.97)	0.60 (0.18,1.89)	**ALED10 +HRT**																
ETID200	0.25 (0.01,2.51)	0.41 (0.02,4.43)	0.64 (0.03,7.70)	0.34 (0.01,3.36)	0.58 (0.02,7.37)	**ETID200**															
ETID400	0.99 (0.51,1.88)	1.65 (0.65,4.12)	2.52 (0.70,9.14)	1.32 (0.65,2.70)	2.19 (0.57,9.02)	3.95 (0.35,96.79)	**ETID400**														
ETID400 +HRT	0.68 (0.03,9.60)	1.12 (0.05,17.18)	1.75 (0.07,30.75)	0.92 (0.04,13.06)	1.47 (0.06,33.97)	2.79 (0.06,121.20)	0.69 (0.04,9.99)	**ETID400 +HRT**													
ETID400 +PHOD2	0.71 (0.30,1.71)	1.18 (0.39,3.46)	1.81 (0.46,7.42)	0.95 (0.38,2.42)	1.58 (0.37,7.07)	2.83 (0.23,71.96)	0.72 (0.30,1.70)	1.05 (0.07,22.94)	**ETID400 +PHOD2**												
RISD2.5	0.45 (0.02,6.25)	0.74 (0.03,10.96)	1.13 (0.04,19.43)	0.60 (0.02,8.56)	1.02 (0.03,17.98)	1.79 (0.46,7.50)	0.44 (0.02,7.01)	0.64 (0.01,36.83)	0.62 (0.02,10.19)	**RISD2.5**											
RISD5	0.84 (0.57,1.13)	1.38 (0.66,2.88)	2.14 (0.67,6.87)	1.12 (0.71,1.71)	1.85 (0.56,6.44)	3.30 (0.32,84.45)	0.84 (0.40,1.74)	1.23 (0.09,26.08)	1.18 (0.45,3.00)	1.88 (0.13,49.76)	**RISD5**										
IBAD2.5	1.06 (0.61,1.78)	1.76 (0.74,4.04)	2.69 (0.77,9.20)	1.41 (0.80,2.54)	2.34 (0.66,8.70)	4.23 (0.39,98.69)	1.06 (0.47,2.50)	1.57 (0.10,33.53)	1.49 (0.53,4.17)	2.39 (0.16,62.23)	1.26 (0.69,2.41)	**IBAD2.5**									
IBAM100	0.99 (0.44,2.22)	1.64 (0.57,4.74)	2.53 (0.63,10.05)	1.32 (0.58,3.03)	2.20 (0.54,9.35)	4.02 (0.34,101.30)	1.00 (0.36,2.86)	1.47 (0.09,33.47)	1.40 (0.41,4.61)	2.26 (0.14,62.94)	1.18 (0.50,2.91)	0.94 (0.47,1.89)	**IBAM100**								
IBAM150	0.97 (0.49,1.91)	1.61 (0.61,4.18)	2.49 (0.68,9.23)	1.30 (0.67,2.57)	2.16 (0.58,8.51)	3.96 (0.35,95.79)	0.98 (0.38,2.51)	1.44 (0.09,31.90)	1.37 (0.45,4.05)	2.20 (0.14,58.95)	1.16 (0.56,2.51)	0.92 (0.48,1.75)	0.98 (0.48,1.99)	**IBAM150**							
IBAQ3	0.67 (0.26,1.67)	1.12 (0.35,3.51)	1.71 (0.40,7.49)	0.89 (0.34,2.34)	1.48 (0.34,6.91)	2.69 (0.22,67.62)	0.67 (0.22,2.13)	1.00 (0.06,22.84)	0.94 (0.26,3.44)	1.51 (0.09,43.80)	0.80 (0.30,2.21)	0.63 (0.29,1.36)	0.67 (0.24,1.91)	0.69 (0.26,1.88)	**IBAQ3**						
ZOLY5	0.73 (0.43,1.26)	1.21 (0.52,2.87)	1.87 (0.55,6.55)	0.97 (0.54,1.86)	1.62 (0.46,6.09)	2.91 (0.28,72.38)	0.74 (0.32,1.71)	1.08 (0.07,23.48)	1.03 (0.37,2.90)	1.64 (0.11,44.88)	0.86 (0.49,1.74)	0.69 (0.33,1.50)	0.74 (0.28,1.99)	0.75 (0.32,1.82)	1.09 (0.38,3.23)	**ZOLY5**					
ZOLY5 +TERD20	0.39 (0.08,1.63)	0.64 (0.12,3.16)	1.00 (0.15,6.36)	0.52 (0.11,2.32)	0.85 (0.13,5.72)	1.49 (0.11,41.49)	0.39 (0.07,1.92)	0.57 (0.02,17.64)	0.54 (0.09,2.95)	0.86 (0.04,26.83)	0.47 (0.09,2.08)	0.37 (0.07,1.74)	0.39 (0.06,2.13)	0.40 (0.07,2.04)	0.58 (0.10,3.21)	0.54 (0.12,2.06)	**ZOLY5 +TERD20**				
MIND1	0.55 (0.22,1.31)	0.91 (0.33,2.54)	1.39 (0.37,5.49)	0.74 (0.28,1.85)	1.21 (0.28,5.55)	2.20 (0.18,55.18)	0.56 (0.18,1.59)	0.82 (0.05,19.24)	0.78 (0.22,2.63)	1.25 (0.07,35.63)	0.66 (0.25,1.67)	0.52 (0.18,1.45)	0.55 (0.16,1.85)	0.57 (0.18,1.72)	0.82 (0.22,2.94)	0.76 (0.26,2.05)	1.41 (0.25,8.74)	**MIND1**			
CLOD800	0.60 (0.02,6.96)	0.98 (0.03,12.84)	1.53 (0.04,23.78)	0.80 (0.02,9.67)	1.33 (0.03,22.25)	2.35 (0.04,119.30)	0.60 (0.02,7.93)	0.80 (0.01,47.10)	0.84 (0.02,12.11)	1.34 (0.02,82.47)	0.72 (0.02,8.80)	0.57 (0.02,7.14)	0.61 (0.02,8.01)	0.62 (0.02,7.87)	0.90 (0.03,12.59)	0.82 (0.02,10.20)	1.58 (0.03,27.23)	1.09 (0.03,15.39)	**CLOD800**		
TILM350	0.70 (0.28,1.66)	1.17 (0.39,3.57)	1.78 (0.44,7.54)	0.94 (0.37,2.38)	1.56 (0.36,7.23)	2.80 (0.23,78.52)	0.71 (0.23,2.12)	1.04 (0.06,22.87)	0.99 (0.28,3.41)	1.58 (0.09,48.26)	0.84 (0.32,2.18)	0.66 (0.23,1.85)	0.70 (0.22,2.35)	0.72 (0.24,2.21)	1.06 (0.28,3.74)	0.96 (0.34,2.62)	1.79 (0.32,11.19)	1.27 (0.36,4.63)	1.16 (0.09,42.46)	**TILM350**	
TILM1400	0.48 (0.17,1.21)	0.79 (0.25,2.54)	1.22 (0.27,5.26)	0.64 (0.23,1.74)	1.06 (0.24,4.91)	1.95 (0.15,55.90)	0.48 (0.15,1.49)	0.70 (0.04,15.49)	0.67 (0.18,2.47)	1.09 (0.06,33.67)	0.57 (0.20,1.60)	0.45 (0.15,1.33)	0.48 (0.13,1.70)	0.49 (0.15,1.59)	0.71 (0.18,2.68)	0.66 (0.21,1.92)	1.23 (0.22,7.97)	0.87 (0.24,3.30)	0.79 (0.06,30.89)	0.68 (0.25,1.88)	**TILM1400**

Green cell with bolded black font indicates significant preventive effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year, TERD20=teriparatide 20 µg/day, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Prior bisphosphonate experience

The network investigating the odds of non-vertebral fracture among studies that restricted participants to those with no prior bisphosphonate experience contained 18 studies and 13 treatments (total 14165 participants) (80, 82, 85, 86, 90, 117, 128, 137, 146-148, 151, 152, 155, 156, 160, 165, 166). Most comparisons involved alendronate or etidronate compared to placebo (4 direct comparisons each). No significant comparisons were found, including alendronate 10 mg/day compared to placebo (OR 0.82, 95% CrI: 0.64, 1.05). A meta-analysis was conducted for studies enrolling only women with prior bisphosphonate experience, based on two studies (total 1165 participants) comparing placebo to alendronate 10 mg/day: the FLEX trial, and a study that recruited women treated with alendronate 10 mg/day for at least three years (161). The meta-analysis showed a non-significant 2% reduction in odds of fracture (OR 0.98, 95% CrI: 0.72, 1.33). Alendronate 10 mg/day showed significant efficacy in reducing non-vertebral fractures in the main analysis, but similar efficacy was not observed when studies were divided by participant treatment experience.

Figure 4.13: Network diagram for non-vertebral fractures (bisphosphonate-naïve)

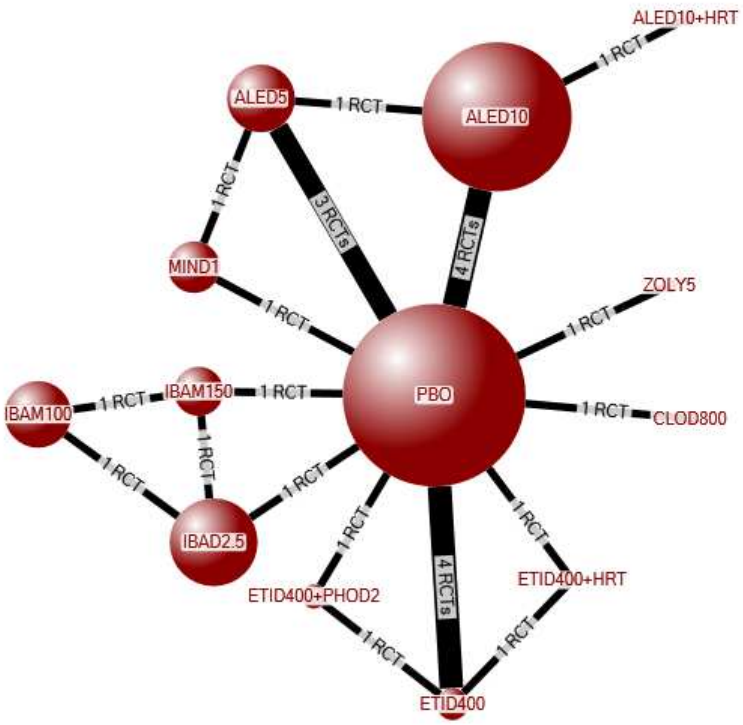


Table 4.26: Staircase diagram for non-vertebral fractures (bisphosphonate-naïve)

PBO	**PBO**												
ALED5	0.99 (0.60,1.58)	**ALED5**											
ALED10	0.82 (0.64,1.05)	0.83 (0.49,1.44)	**ALED10**										
ALED10 +HRT	0.23 (0.001,3.61)	0.23 (0.001,3.86)	0.27 (0.001,4.30)	**ALED10 +HRT**									
ETID400	1.06 (0.56,1.94)	1.07 (0.47,2.39)	1.28 (0.64,2.49)	4.79 (0.27,1104)	**ETID400**								
ETID400 +HRT	0.69 (0.04,8.16)	0.69 (0.04,9.03)	0.83 (0.05,10.21)	3.15 (0.06,1512)	0.63 (0.04,7.90)	**ETID400 +HRT**							
ETID400 +PHOD2	0.73 (0.33,1.60)	0.74 (0.30,1.90)	0.88 (0.39,2.05)	3.28 (0.17,829.8)	0.70 (0.31,1.60)	1.07 (0.08,20.31)	**ETID400 +PHOD2**						
IBAD2.5	1.11 (0.70,1.74)	1.12 (0.58,2.24)	1.35 (0.80,2.24)	4.93 (0.29,1121)	1.04 (0.50,2.32)	1.61 (0.13,31.24)	1.51 (0.62,3.74)	**IBAD2.5**					
IBAM100	1.09 (0.51,2.51)	1.12 (0.46,2.90)	1.33 (0.59,3.11)	5.00 (0.26,1190)	1.04 (0.40,2.92)	1.59 (0.12,35.87)	1.50 (0.51,4.61)	0.99 (0.53,1.97)	**IBAM100**				
IBAM150	1.12 (0.50,2.66)	1.14 (0.45,3.08)	1.37 (0.58,3.24)	5.06 (0.28,1201)	1.07 (0.40,3.04)	1.65 (0.11,37.59)	1.53 (0.52,4.68)	1.02 (0.51,2.14)	1.03 (0.54,1.93)	**IBAM150**			
ZOLY5	0.24 (0.02,2.07)	0.25 (0.02,2.26)	0.30 (0.02,2.60)	1.09 (0.02,237.4)	0.23 (0.02,2.26)	0.37 (0.01,14.57)	0.33 (0.03,3.24)	0.22 (0.02,2.00)	0.22 (0.02,2.29)	0.21 (0.02,2.27)	**ZOLY5**		
MIND1	0.64 (0.28,1.46)	0.65 (0.27,1.60)	0.78 (0.33,1.82)	3.03 (0.15,743.3)	0.62 (0.22,1.64)	0.96 (0.07,21.12)	0.89 (0.28,2.73)	0.58 (0.23,1.50)	0.58 (0.19,1.80)	0.56 (0.19,1.78)	2.60 (0.27,37.58)	**MIND1**	
CLOD800	0.60 (0.04,6.71)	0.60 (0.03,7.27)	0.72 (0.04,8.27)	2.97 (0.04,775.9)	0.57 (0.03,6.87)	0.82 (0.02,50.19)	0.80 (0.05,10.36)	0.53 (0.03,6.34)	0.54 (0.03,6.74)	0.53 (0.03,6.52)	2.38 (0.06,85.90)	0.93 (0.05,12.06)	**CLOD800**

PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day.

Treatment durations

Fifteen studies provided data for one year of treatment (86, 91, 96, 121, 125, 128, 133, 144, 152, 153, 155, 157, 158, 162, 164), 21 studies for two years of treatment (84, 95, 120, 124, 128, 133, 134, 137, 141, 144, 147, 150, 151, 156, 160, 161, 163, 167), 10 studies for three years of treatment (82, 86, 90, 117, 125, 133, 144, 146, 159, 166), and 2 studies for both four years (136, 148) and five years of treatment (87, 144). The data for two years contributed to two networks: a larger NMA containing 19 studies and 14 treatments, and a smaller NMA containing two studies and four treatments (154, 165).

Alendronate 10 mg/day was superior to placebo in both the main analysis (OR 0.78, 95% CrI: 0.60, 0.98) and the analysis of first-year data (OR 0.52, 95% CrI: 0.29, 0.90), but not in second-, third-, or fifth-year data. No study provided data for alendronate at four years of treatment. The main analysis included 13 studies assessing alendronate 10 mg/day, the first-year analysis included five studies, both the second and third-year analyses included three, and the fifth-year analysis included only one.

Daily risedronate 2.5 mg (OR 0.46, 95% CrI: 0.12,1.49) and 5 mg (OR 0.83, 95% CrI: 0.58,1.11) showed non-significant reductions in odds of fracture compared to placebo in the main analysis and first-year analysis, but became significant among studies with two years of treatment (OR 0.56, 95% CrI: 0.30,0.95 for 2.5 mg dose, and OR 0.63, 95% CrI: 0.41,0.96 for 5 mg dose). The main analysis included 2 studies for 2.5 mg/day and 6 studies for 5 mg/day, the first-year analysis included three studies for 2.5 mg/day and two studies for 5 mg/day, while the second-year analysis included three and five studies, respectively, for the 2.5 mg and 5 mg doses. No other bisphosphonate had statistically significant results for the reduction of non-vertebral fractures compared to placebo or to other treatments.

Table 4.27: Staircase diagram for non-vertebral fractures (1 year)

PBO	**PBO**									
ALED5	0.82 (0.51,1.33)	**ALED5**								
ALED10	**0.52 (0.29,0.90)**	0.63 (0.29,1.27)	**ALED10**							
ETID200	0.50 (0.11,2.06)	0.62 (0.13,2.72)	0.97 (0.20,4.54)	**ETID200**						
RISD2.5	0.87 (0.51,1.54)	1.07 (0.53,2.17)	1.69 (0.79,3.83)	1.73 (0.46,6.95)	**RISD2.5**					
RISD5	0.74 (0.42,1.32)	0.90 (0.44,1.86)	1.43 (0.66,3.29)	1.47 (0.35,6.85)	0.85 (0.46,1.50)	**RISD5**				
IBAM150	0.65 (0.26,1.66)	0.79 (0.29,2.24)	1.26 (0.59,2.87)	1.32 (0.24,7.51)	0.75 (0.27,2.24)	0.89 (0.31,2.65)	**IBAM150**			
ZOLY5	0.84 (0.50,1.36)	1.03 (0.50,1.98)	1.62 (0.76,3.44)	1.67 (0.37,7.90)	0.96 (0.46,1.98)	1.14 (0.53,2.35)	1.30 (0.44,3.62)	**ZOLY5**		
ZOLY5 +TERD20	0.45 (0.10,1.76)	0.55 (0.11,2.34)	0.87 (0.17,3.95)	0.86 (0.12,7.37)	0.52 (0.10,2.25)	0.61 (0.12,2.64)	0.69 (0.11,3.50)	0.54 (0.13,1.93)	**ZOLY5 +TERD20**	
MIND1	0.36 (0.04,2.06)	0.45 (0.05,2.36)	0.70 (0.07,4.47)	0.72 (0.05,6.99)	0.42 (0.04,2.43)	0.50 (0.05,3.05)	0.54 (0.05,4.05)	0.44 (0.05,2.73)	0.81 (0.06,8.65)	**MIND1**

Green cell with bolded black font indicates significant preventive effect.PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, ETID200=etidronate 200 mg/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAM150=ibandronate 150 mg/month, ZOLY5=zoledronic acid 5 mg/year, TERD20=teriparatide 20 µg/day, MIND1=minodronate 1 mg/day.

Table 4.28: Staircase diagram for non-vertebral fractures (2 years, small NMA)

IBAD2.5	**IBAD2.5**			
IBAM100	1.01 (0.37,2.86)	**IBAM100**		
IBAM150	1.04 (0.37,3.04)	1.05 (0.36,2.99)	**IBAM150**	
IBAQ3	0.63 (0.23,1.80)	0.63 (0.15,2.70)	0.60 (0.14,2.70)	**IBAQ3**

IBAD2.5=ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150= ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months

Table 4.29: Staircase diagram for non-vertebral fractures (2 years, large NMA)

PBO	**PBO**												
ALED5	0.85 (0.48,1.45)	**ALED5**											
ALED5 +ALFD1	0.56 (0.19,1.60)	0.66 (0.27,1.61)	**ALED5 +ALFD1**										
ALED10	0.55 (0.16,1.97)	0.65 (0.17,2.59)	1.00 (0.19,5.36)	**ALED10**									
ALED10 +HRT	0.39 (0.10,1.45)	0.46 (0.11,1.86)	0.70 (0.13,3.71)	0.69 (0.19,2.49)	**ALED10 +HRT**								
ETID200	0.25 (0.01,2.81)	0.29 (0.01,3.38)	0.45 (0.02,6.04)	0.43 (0.02,6.43)	0.60 (0.02,10.13)	**ETID200**							
ETID400	0.93 (0.45,1.94)	1.09 (0.44,2.69)	1.65 (0.46,5.95)	1.68 (0.39,6.99)	2.40 (0.52,11.00)	3.74 (0.30,96.48)	**ETID400**						
ETID400 +PHOD2	0.69 (0.28,1.67)	0.81 (0.28,2.33)	1.22 (0.30,5.05)	1.26 (0.26,5.54)	1.80 (0.36,8.58)	2.82 (0.21,71.96)	0.74 (0.30,1.79)	**ETID400 +PHOD2**					
RISD2.5	**0.56 (0.30,0.95)**	0.65 (0.30,1.43)	0.99 (0.31,3.23)	1.00 (0.24,3.98)	1.45 (0.33,6.19)	2.21 (0.19,67.06)	0.60 (0.24,1.47)	0.81 (0.27,2.25)	**RISD2.5**				
RISD5	**0.63 (0.41,0.96)**	0.73 (0.38,1.52)	1.11 (0.36,3.50)	1.12 (0.29,4.29)	1.63 (0.40,6.69)	2.53 (0.21,66.40)	0.67 (0.29,1.56)	0.90 (0.34,2.43)	1.11 (0.65,2.05)	**RISD5**			
ZOLY5	0.27 (0.02,2.16)	0.31 (0.02,2.73)	0.48 (0.03,5.35)	0.46 (0.03,5.70)	0.67 (0.04,8.66)	1.05 (0.04,52.30)	0.29 (0.02,2.66)	0.38 (0.03,3.83)	0.48 (0.03,4.14)	0.43 (0.03,3.59)	**ZOLY5**		
MIND1	0.70 (0.25,1.93)	0.81 (0.26,2.67)	1.23 (0.29,5.66)	1.25 (0.25,6.14)	1.79 (0.35,9.73)	2.84 (0.21,77.28)	0.75 (0.21,2.63)	1.02 (0.26,3.94)	1.25 (0.39,4.19)	1.12 (0.36,3.43)	2.64 (0.25,39.80)	**MIND1**	
TILM350	0.72 (0.29,1.68)	0.84 (0.29,2.36)	1.29 (0.31,5.04)	1.29 (0.27,6.26)	1.85 (0.37,8.98)	2.91 (0.23,86.98)	0.76 (0.25,2.41)	1.04 (0.30,3.65)	1.27 (0.45,3.82)	1.15 (0.42,3.09)	2.66 (0.27,41.04)	1.03 (0.26,3.86)	**TILM350**
TILM1400	0.48 (0.18,1.21)	0.56 (0.18,1.71)	0.84 (0.21,3.66)	0.85 (0.18,4.20)	1.21 (0.25,6.35)	1.94 (0.14,50.87)	0.51 (0.16,1.68)	0.69 (0.18,2.53)	0.84 (0.28,2.67)	0.76 (0.26,2.17)	1.79 (0.18,27.71)	0.69 (0.17,2.65)	0.66 (0.24,1.82)

Green cells with bolded black font indicate significant preventive effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Table 4.30: Staircase diagram for non-vertebral fractures (3 years)

PBO	**PBO**							
ALED5	0.61 (0.11,2.60)	**ALED5**						
ALED10	0.76 (0.46,1.21)	1.24 (0.28,7.25)	**ALED10**					
ETID400	0.78 (0.18,3.32)	1.29 (0.16,12.65)	1.04 (0.22,4.68)	**ETID400**				
RISD5	0.89 (0.55,1.28)	1.43 (0.31,8.68)	1.17 (0.60,2.10)	1.12 (0.25,5.09)	**RISD5**			
IBAD2.5	1.11 (0.56,2.26)	1.82 (0.37,11.91)	1.46 (0.65,3.48)	1.42 (0.29,7.37)	1.25 (0.59,3.04)	**IBAD2.5**		
ZOLY5	0.73 (0.38,1.41)	1.19 (0.25,7.75)	0.96 (0.43,2.21)	0.93 (0.19,4.61)	0.82 (0.41,1.91)	0.66 (0.25,1.70)	**ZOLY5**	
CLOD800	0.59 (0.02,7.29)	0.97 (0.03,20.18)	0.77 (0.03,10.07)	0.74 (0.02,14.09)	0.67 (0.03,8.49)	0.52 (0.02,7.12)	0.81 (0.03,10.84)	**CLOD800**

PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month or 150 mg/month, IBAD2.5=ibandronate 2.5 mg/day, ZOLY5=zoledronic acid 5 mg/year, CLOD800=clodronate 800 mg/day.

Table 4.31: Staircase diagram for non-vertebral fractures (4 years)

PBO	**PBO**		
ETID400	0.62 (0.14,2.66)	**ETID400**	
ETID400 +HRT	0.65 (0.03,8.72)	1.05 (0.04,15.35)	**ETID400 +HRT**

PBO=placebo, ETID400=etidronate 400 mg/day, HRT=hormone replacement therapy.

Table 4.32: Staircase diagram for non-vertebral fractures (5 years)

PBO	**PBO**		
ALED10	0.99 (0.38,2.63)	**ALED10**	
RISD5	0.66 (0.25,1.82)	0.66 (0.16,2.70)	**RISD5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, RISD5=risedronate 5 mg/day.

4.3.6.3 SENSITIVITY ANALYSES

Baseline denominators

No significant changes were found compared to the main analysis when the numbers of randomized participants were used as the denominators of effect estimates instead of the total analyzable population. Only alendronate 10 mg/day was significantly better than placebo in reducing non-vertebral fractures (OR 0.78, 95% CrI: 0.60, 0.97).

Low risk of bias

The network included 24 studies (24823 participants) judged low risk of bias for incomplete efficacy outcome data (85-87, 90, 91, 96, 121, 125, 128, 134, 147, 148, 152, 153, 155-158, 160-165). The earliest study was published in 1990 and the most recent in 2012. The study durations ranged from 48 weeks to 5 years. There were 6 primary prevention studies and 18 secondary prevention studies. Like the main results, alendronate 10 mg/day showed greater efficacy than placebo for preventing non-vertebral fractures (OR 0.81, 95% CrI: 0.63, 0.96). In addition, zoledronic acid with teriparatide 20 µg/day showed significantly greater efficacy than alendronate 5 mg/day (OR 0.23, 95% CrI: 0.04, 0.94) which was not observed in the main analysis (OR 0.44, 95% CrI: 0.09, 1.90). There are no studies that directly assessed alendronate against zoledronic acid combined with teriparatide. One study compared zoledronic acid to its combination with teriparatide which was included in both analyses. Thus, the difference in effect likely lies in the inclusion of six studies assessing alendronate 5 mg/day in the main analysis and two studies in the sensitivity analysis. Both studies included in the sensitivity analysis showed lower efficacy of alendronate 5 mg/day, which may have translated to greater efficacy of zoledronic acid combined with teriparatide. Alternatively, the zoledronic acid combination treatment may have shown greater efficacy among trials with low risk of bias and higher methodological quality compared to all trials included in the main analysis.

Approved bisphosphonates

Thirty-nine of 43 studies were included in the network that only examined non-vertebral fracture prevention among the five widely approved bisphosphonates (total 44270 participants), and four studies were excluded that contained comparisons to clodronate (146), tiludronate (120) and minodronate (137, 155). When compared to the main analysis, there were no changes in significance. Alendronate at 10 mg/day compared to placebo is the only significant comparison (OR 0.78, 95% CrI: 0.60, 0.97).

Fracture as efficacy outcome

All studies in the network MA that assessed studies with fracture as an efficacy outcome (11 studies, total 32329 participants) contained two treatment arms, and all except one are placebo comparisons (84-86, 90, 117, 125, 133, 137, 141, 144, 159). The study by Orimo et al. (2011) provided the only head-to-head comparison of alendronate 5 mg/day against alendronate 5 mg/day with alfacalcidol 1 µg/day.

The publication years ranged from 1995 to 2014 and the study lengths ranged between two to five years. None of the treatments were significantly more effective than placebo or one another. Alendronate 10 mg/day was no longer significant in the sensitivity analysis (OR 0.82, 95% CrI: 0.56, 1.19). While the main analysis included 13 studies with the treatment arm alendronate 10 mg/day, the sensitivity analysis included 3 studies with direct comparisons. The decreased number of direct comparisons may have affected the sample size and precision of the estimate, and may have contributed wider credible intervals in the sensitivity analysis.

Change in criteria for primary and secondary prevention

Based on the re-classification using 2.5 instead of 2 as the threshold for BMD and T-score values, two previously secondary studies were re-classified as primary prevention studies (96, 152). Both studies specified in the inclusion criteria that participants must have BMD at least two SD below the

peak bone mass and were included in the main analysis as secondary studies. However, the new criteria for secondary prevention specify 2.5 SD or more below the peak bone mass, thus the next hierarchical item was examined. Both studies excluded participants with prevalent vertebral fractures, causing them to be classified as primary prevention studies. All other studies remained the same under the new classification criteria.

Primary prevention studies

After adding two studies, the NMA was re-analyzed containing eleven primary studies (total 7286 participants). No significant differences were detected in comparison to results of the subgroup analysis for primary prevention studies.

Secondary prevention studies

Excluding two studies re-classified as primary prevention studies, the sensitivity analysis included 32 studies (total 38493 participants). Results of the sensitivity analysis were compared to the subgroup analysis including only secondary studies. No significant differences were found between the subgroup and sensitivity analysis, indicating changing the threshold for classifying primary and secondary studies did not significantly impact estimates of the subgroup analysis.

4.3.7 HIP FRACTURES

4.3.7.1 MAIN ANALYSIS

The network meta-analysis for hip fractures included 15 studies (31544 participants), of which two were primary prevention trials and thirteen were secondary prevention trials (85-88, 90, 117, 125, 131, 136, 147, 154, 159, 162, 168, 169). The publication years ranged from 1990 to 2013, and the study duration from 1 to 5 years. The only treatment significantly more effective than placebo at reducing the likelihood of hip fractures was zoledronic acid 5 mg/year (OR 0.55, 95% CrI: 0.34, 0.85). No other bisphosphonate or bisphosphonate combination was found to be significantly better than placebo or other treatments. Due to the relatively small number of included studies, most comparisons except for alendronate 10 mg/day were supported by no more than two studies.

Figure 4.14: Network diagram for hip fractures

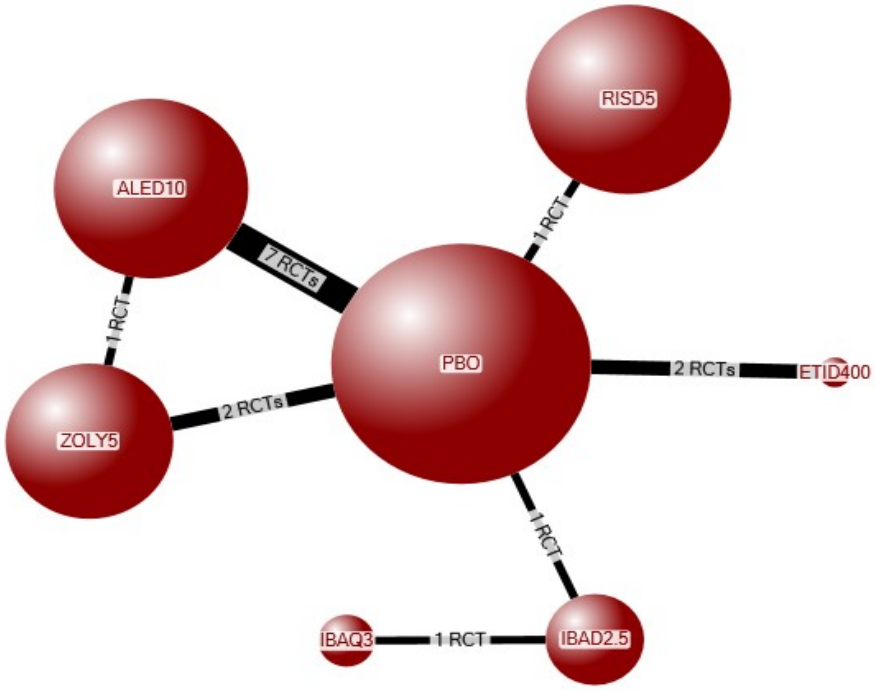


Table 4.33: Staircase diagram for hip fractures

PBO	**PBO**						
ALED10	0.68 (0.44,1.00)	**ALED10**					
ETID400	0.87 (0.14,5.05)	1.31 (0.20,7.65)	**ETID400**				
RISD5	0.73 (0.43,1.23)	1.08 (0.57,2.11)	0.85 (0.14,5.74)	**RISD5**			
IBAD2.5	1.44 (0.42,5.87)	2.12 (0.60,9.08)	1.67 (0.19,17.41)	1.97 (0.52,8.61)	**IBAD2.5**		
IBAQ3	0.55 (0.02,7.37)	0.82 (0.03,11.49)	0.66 (0.01,16.25)	0.76 (0.03,10.69)	0.38 (0.02,3.72)	**IBAQ3**	
ZOLY5	**0.55 (0.34,0.85)**	0.82 (0.45,1.47)	0.64 (0.11,4.16)	0.76 (0.37,1.47)	0.38 (0.09,1.42)	0.99 (0.07,28.24)	**ZOLY5**

Green cell with bolded black font indicates significant preventive effect.PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5=ibandronate 2.5 mg/day, IBAQ3=ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year.

4.3.7.2 SUBGROUP ANALYSES

Primary and secondary prevention

Of the 15 studies that reported hip fracture data among participants, two studies (4534 participants) were classified as primary prevention (85, 169). The first primary prevention study was the Clinical Fracture Arm of the FIT study which assessed alendronate 10 mg/day against placebo. It showed lower hip fracture events in the alendronate group (19/2214, 0.9%) compared to the placebo group (24/2218, 1%). The second primary prevention study was an open-label study comparing alendronate 10 mg/day (1/42, 5%) and zoledronic acid 5 mg/year (0/59) with slightly lower rates of fracture in the zoledronic acid arm.

Thirteen studies were included in the network meta-analysis of secondary studies (total 27010 participants) (86-88, 90, 117, 125, 131, 136, 147, 154, 159, 162, 168). As in the main analysis, zoledronic acid 5 mg/year showed a statistically significant reduction in odds of hip fractures compared to placebo (OR 0.57, 95% CrI: 0.34, 0.94). In addition, alendronate 10 mg/day also

showed a significant reduction in odds of hip fracture compared to placebo (OR 0.60, 95% CrI: 0.35, 0.98) whereas it was not better than placebo in the main analysis (OR 0.58, 95% CrI: 0.44, 1.00). This suggests while zoledronic acid appears to be effective for reducing the likelihood of hip fractures in all populations regardless of osteoporosis severity, the efficacy of alendronate 10 mg/day may be slightly affected by the severity of patient population.

Figure 4.15: Network diagram for hip fractures (secondary prevention)

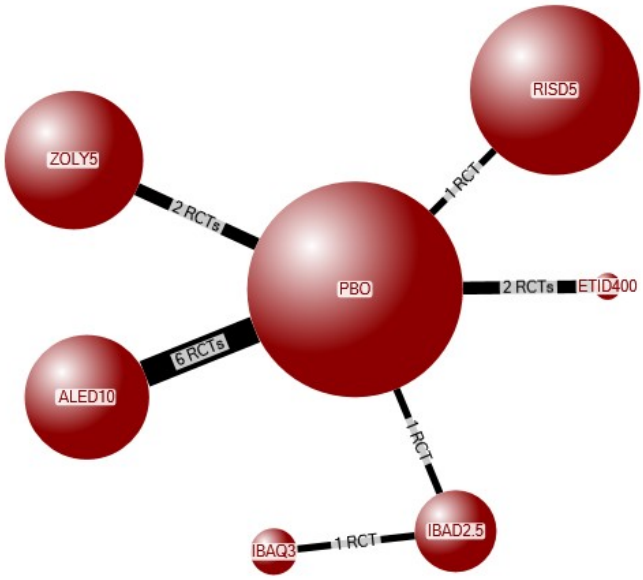


Table 4.34: Staircase diagram for hip fractures (secondary prevention)

PBO	**PBO**						
ALED10	**0.60 (0.35,0.98)**	**ALED10**					
ETID400	0.87 (0.12,4.45)	1.44 (0.19,8.11)	**ETID400**				
RISD5	0.72 (0.41,1.29)	1.20 (0.59,2.67)	0.83 (0.15,6.09)	**RISD5**			
IBAD2.5	1.51 (0.37,5.85)	2.47 (0.58,11.30)	1.68 (0.22,18.24)	2.08 (0.45,9.15)	**IBAD2.5**		
IBAQ3	0.54 (0.02,7.41)	0.90 (0.04,12.39)	0.65 (0.01,18.77)	0.74 (0.03,10.74)	0.38 (0.02,3.68)	**IBAQ3**	
ZOLY5	**0.57 (0.34,0.94)**	0.95 (0.47,1.96)	0.66 (0.12,4.95)	0.79 (0.36,1.67)	0.38 (0.09,1.65)	1.05 (0.07,26.38)	**ZOLY5**

Green cells with bolded black font indicate significant preventive effect.PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, IBAD2.5=ibandronate 2.5 mg/day, IBAQ3=ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year.

Prior bisphosphonate experience

Six studies included only participants with no prior bisphosphonate treatments (total 9942 participants), ranging from the years 1990 to 2004. The study durations ranged from two to four years. Zoledronic acid could not be evaluated. Alendronate 10 mg/day became statistically significant compared to placebo (OR 0.57, 95% CrI: 0.31, 0.97), whereas it was previously not significant in the main analysis (OR 0.68, 95% CrI: 0.44, 1.00). This may indicate alendronate 10 mg/day has higher efficacy in bisphosphonate-naïve populations compared to the general population. Only the FLEX study recruited participants with previous bisphosphonate experience. All participants in FLEX previously received at least three years of alendronate treatment. Descriptively, the event rate of hip fractures in the placebo arm (13/437, 3%) is similar to the event rate in the alendronate 10 mg/day arm (20/662, 3%).

Figure 4.16: Network diagram for hip fractures (bisphosphonate-naïve)

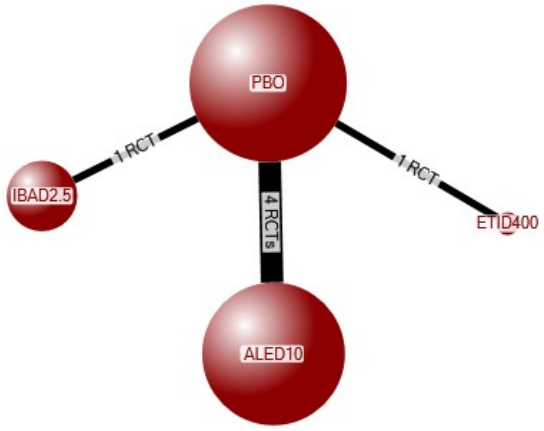


Table 4.35: Staircase diagram for hip fractures (bisphosphonate-naïve)

PBO	**PBO**			
ALED10	**0.57 (0.31,0.97)**	**ALED10**		
ETID400	2.06 (0.12,58.31)	3.69 (0.21,115.20)	**ETID400**	
IBAD2.5	1.48 (0.36,6.40)	2.60 (0.60,12.77)	0.74 (0.02,16.04)	**IBAD2.5**

Green cell with bolded black font indicates significant preventive effect.
PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week,
ETID400=etidronate 400 mg/day, IBAD2.5=ibandronate 2.5 mg/day.

Treatment durations

Network meta-analyses could not be conducted for one or five years of treatment because only one study was included in each. Two studies were included in the two-year analysis (131, 168), seven in the three-year analysis (86, 88, 90, 117, 125, 159, 169), and two in the fourth-year analysis (85, 136). No treatment was found to be more effective than placebo or other treatments in second-, third-, and fourth-year analyses.

Table 4.36: Staircase diagram for hip fracture (2 years)

PBO	**PBO**		
ALED10	0.46 (0.05,2.94)	**ALED10**	
ZOLY5	0.54 (0.18,1.68)	1.21 (0.14,13.47)	**ZOLY5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ZOLY5=zoledronic acid 5mg/year.

Table 4.37: Staircase diagram for hip fracture (3 years)

PBO	**PBO**			
ALED10	0.46 (0.20,1.01)	**ALED10**		
RISD5	0.72 (0.34,1.58)	1.58 (0.54,4.95)	**RISD5**	
IBAD2.5	1.40 (0.34,6.32)	3.07 (0.62,17.15)	1.94 (0.39,10.31)	**IBAD2.5**
ZOLY5	0.55 (0.22,1.04)	1.18 (0.38,3.22)	0.76 (0.22,1.94)	0.38 (0.07,1.78)	**ZOLY5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, RISD5=risedronate 5 mg/day, IBAD2.5=ibandronate 2.5 mg/day, ZOLY5=zoledronic acid 5 mg/year.

Table 4.38: Staircase diagram for hip fracture (4 years)

PBO	**PBO**		
ALED10	0.28 (0.78,2.28)	**ALED10**	
ETID400	0.02 (0.43,5.38)	0.02 (0.55,8.38)	**ETID400**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day.

4.3.7.3 SENSITIVITY ANALYSES

Baseline denominators

There were no significant changes compared to the main analysis when the total number of randomized participants was used as the denominator. Only zoledronic acid was significantly better than placebo in reducing hip fractures (OR 0.55, 95% CrI: 0.34, 0.85).

Low risk of bias

Seven studies (total 18194 participants) were included in the sensitivity analysis for low risk of bias in the domain of incomplete efficacy data (85-87, 90, 125, 147, 162). Publication years ranged from 1990 to 2007, and study durations ranged from one to five years. Five studies provided data for the treatment alendronate 10 mg/day, and the other two treatments (etidronate 400 mg/day and zoledronic acid 5 mg/year) have one study each included in the network meta-analysis. None of the effect estimates in the sensitivity analysis were significant, including zoledronic acid (OR 0.58, 95% CrI: 0.29, 1.12).

Approved bisphosphonates

All studies in the main analysis examined one of the five main bisphosphonates, thus no sensitivity analysis was conducted.

Fracture as efficacy outcome

A total of 7 studies (total 26955 participants) listed fracture as a primary efficacy outcome (85, 86, 90, 117, 125, 131, 159). All were placebo-controlled trials with two arms. Three studies examined alendronate 10 mg/day, and two assessed the efficacy of zoledronic acid 5 mg/year. Due to a smaller number of included studies compared to the main analysis, many comparisons were not assessable in the sensitivity analysis. Treatment comparisons in the sensitivity analysis did not differ

substantially from the main analysis. Zoledronic acid at a dosage of 5 mg/year remains significantly better than placebo at reducing hip fracture incidence among postmenopausal women (OR 0.57, 95% CrI: 0.34, 0.95). The credible interval is slightly wider in the sensitivity analysis compared to the main analysis.

Change in criteria for primary and secondary prevention

Based on the re-classification using the BMD and T-score thresholds of 2.5 instead of 2, none of the included studies which reported clinical vertebral fracture changed in prevention trial type. All studies previously categorized as secondary or primary remained classified as the same type of prevention study. This indicates that the shift in thresholds did not significantly impact the classification of studies into primary or secondary prevention compared to thresholds from previous reviews used in the main analysis.

4.3.8 WRIST FRACTURES

4.3.8.1 MAIN ANALYSIS

Of the nine studies included in the network for wrist fractures (total 12005 participants), two are primary prevention studies and seven are secondary prevention studies (85, 86, 88, 97, 126, 133, 136, 162, 167). Publication ranged from 1996 to 2012 and treatment duration from one to four years. All were two-arm, placebo-controlled trials, except one with alendronate and zoledronic acid. None of the treatments were significantly better than any comparator at preventing wrist fractures. Inconsistency was detected within the placebo and alendronate 10 mg/day arms of the study by Greenspan et al. (1998). Potential causes of inconsistency may smaller sample size and patients with lower disease severity (Appendix 8). No substantial differences were found in a sensitivity analysis excluding the study (Appendix 8).

Figure 4.17: Network diagram for wrist fractures

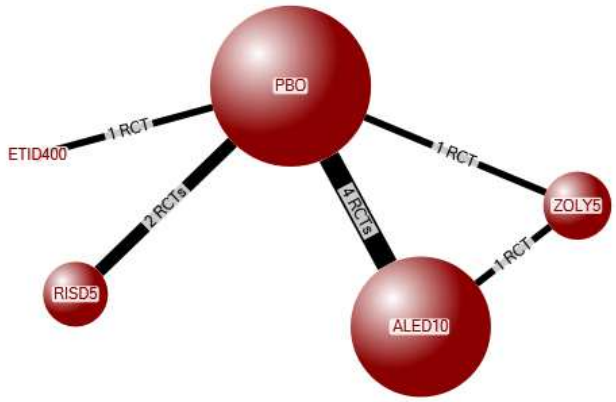


Table 4.39: Staircase diagram for wrist fractures

PBO	**PBO**				
ALED10	0.81 (0.44,1.49)	**ALED10**			
ETID400	0.91 (0.09,8.04)	1.12 (0.10,10.75)	**ETID400**		
RISD5	0.59 (0.20,1.66)	0.73 (0.21,2.43)	0.66 (0.06,8.18)	**RISD5**	
ZOLY5	0.19 (0.02,1.04)	0.23 (0.02,1.31)	0.20 (0.01,3.67)	0.31 (0.02,2.46)	**ZOLY5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, RISD5=risedronate 5 mg/day, ZOLY5=zoledronic acid 5 mg/year.

4.3.8.2 SUBGROUP ANALYSES

Primary and secondary prevention

The two primary prevention studies (total 4602 participants) included the Clinical Fracture Arm of the FIT study comparing alendronate 10 mg/day to placebo, and a smaller study comparing placebo to risedronate 5 mg/day (167). The results demonstrated no treatment was better than placebo in reducing wrist fractures. Seven secondary prevention studies (total 7403 participants) were included in the network (86, 88, 97, 126, 133, 136, 162). The subgroup analysis showed zoledronic acid was

more effective than placebo at reducing wrist fracture (OR 0.17, 95% CrI: 0.02, 0.96), whereas the main analysis did not show significance in this comparison (OR 0.19, 95% CrI: 0.02, 1.04). No other treatments demonstrated greater efficacy than placebo or other bisphosphonates.

Figure 4.18: Network diagram for wrist fracture (primary prevention)

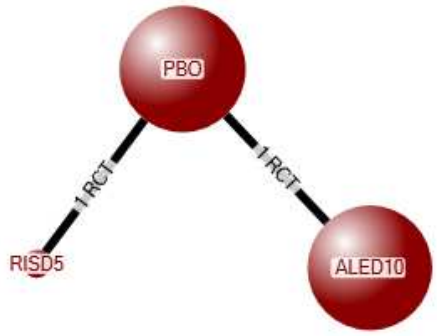


Table 4.40: Staircase diagram for wrist fracture (primary prevention)

PBO	**PBO**		
ALED10	1.19 (0.47,3.03)	**ALED10**	
RISD5	0.40 (0.02,8.51)	0.34 (0.01,8.32)	**RISD5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, RISD5=risedronate 5 mg/day

Figure 4.19: Network diagram for wrist fracture (secondary prevention)

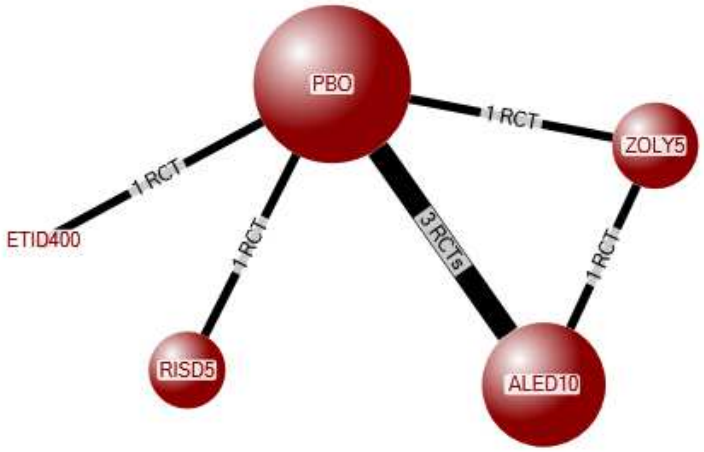


Table 4.41: Staircase diagram for wrist fracture (secondary prevention)

PBO	**PBO**				
ALED10	0.57 (0.31,1.27)	**ALED10**			
ETID400	0.88 (0.10,7.90)	1.54 (0.14,15.06)	**ETID400**		
RISD5	0.62 (0.23,1.77)	1.09 (0.30,3.39)	0.70 (0.06,8.20)	**RISD5**	
ZOLY5	**0.17 (0.02,0.96)**	0.28 (0.04,1.68)	0.18 (0.01,3.36)	0.26 (0.03,2.03)	**ZOLY5**

Green cell with bolded black font indicates significant preventive effect.
PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400= etidronate 400 mg/day, RISD5=risedronate 5 mg/day, ZOLY5=zoledronic acid 5 mg/year.

Prior bisphosphonate experience

Two studies included treatment naïve populations. In the Vertebral Fracture and Clinical Fracture studies of FIT, participants were excluded if they had taken bisphosphonate at any time prior to study entry. Since both studies had the same treatments, comparing alendronate 10 mg/day to placebo, a meta-analysis was conducted using the random-effects model. The resulting estimate showed a non-significant reduction in odds of wrist fractures occurring in participants receiving alendronate 10 mg/day compared to placebo (OR 0.81, 95% CI: 0.36, 1.83). The odds ratio did not differ from results of the main analysis NMA (OR 0.81, CrI: 0.44, 1.49).

The only trial that enrolled participants with prior bisphosphonate treatment experience was the first three-year extension of the HORIZON study. The study included participants who received zoledronic acid 5 mg/year during the core HORIZON study, thus all participants had three years of prior treatment experience. In the extension, they were re-randomized to continued zoledronic acid 5 mg/year or placebo. Participants of the core study who received placebo for three years were given zoledronic acid to maintain blinding, but were not included in the results. Results of the extension study showed lower fracture rates in the zoledronic acid group (1/613, 0.1%) compared to the placebo group (4/616, 0.6%).

Treatment durations

Due to a smaller number of studies that reported wrist fracture, only third-year and fourth-year data were sufficient to conduct network meta-analyses. Four studies (total 5004 participants) provided data at three years (86, 88, 126, 133), and two studies (total 4532 participants) provided data for four years (85, 136). No study reported wrist fracture at five years of treatment, while only one study each provided data for one and two years of treatment. Results at three and four years were not substantially different from the main analysis where no significant comparison was found.

Table 4.42: Staircase diagram for wrist fractures (3 years)

PBO	**PBO**			
ALED10	0.67 (0.30,2.99)	**ALED10**		
RISD5	0.63 (0.17,2.38)	0.94 (0.11,3.79)	**RISD5**	
ZOLY5	0.21 (0.01,2.01)	0.29 (0.01,3.22)	0.33 (0.01,4.52)	**ZOLY5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, RISD5=risedronate 5 mg/day, ZOLY5=zoledronic acid 5 mg/year.

Table 4.43: Staircase diagram for wrist fractures (4 years)

PBO	**PBO**		
ALED10	1.19 (0.46,3.06)	**ALED10**	
ETID400	0.89 (0.09,8.97)	0.75 (0.06,9.05)	**ETID400**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day.

4.3.8.3 SENSITIVITY ANALYSES

Baseline denominators

Compared to the main analysis, the sensitivity analysis including baseline denominators demonstrated no significant differences in effect estimates or credible intervals.

Low risk of bias

Three studies (total 7866 participants) had low risk of bias in the domain of incomplete outcome data (85, 86, 126). No significant results were found, matching findings of the main analysis.

Approved bisphosphonates

No sensitivity analysis was conducted because all studies included one of the five major bisphosphonates.

Fracture as efficacy outcome

Three studies (total 8086 participants) were included in the sensitivity analysis (85, 86, 133). No bisphosphonate was significantly better than a comparator for reducing the likelihood of wrist fractures.

Change in criteria for primary and secondary prevention

The re-classification did not change the prevention type of any of the nine studies, indicating that the shift in thresholds did not significantly impact the classification of studies.

4.3.9 HEALTH-RELATED QUALITY OF LIFE

Quality of life was reported by three trials: Cascella et al. (2005) and companion studies to the HORIZON and ROSE trials (170, 171). In HORIZON, pooled and domain-specific scores of the mini-Osteoporosis Quality of Life Questionnaire (OQOL) were assessed for 1434 of 7765 participants. The instrument has five domains with two questions each and a summary score from 1 to 7, where a lower score indicates lower functioning. Although both treatments showed improvements from baseline, differences were not significant (placebo mean -0.04, SD 1.15; zoledronic acid mean -0.01, SD 0.98). In ROSE, overall and domain-specific scores were reported for the Qualeffo-41 questionnaire for 580 of 604 randomized participants. The questionnaire had a range from 41 to 205 points which can be converted to a score from 1 to 100, where a lower score indicates higher quality of life. Alendronate and zoledronic acid did not show significant improvements in total score from baseline (alendronate mean -0.6, SD 9.0; zoledronic acid mean -1.2, SD 8.8). One trial with 40 participants reported domain-specific scores for SF-36 but did not report a pooled score (132), thus it was not included in the analysis. Changes from baseline reported by ROSE and HORIZON were converted to standardized mean differences and included in an NMA. The network included placebo, zoledronic acid 5 mg/year, and alendronate 10 mg/day given as a weekly dose of 70 mg/week. No significant differences were found between any of the treatments.

Figure 4.20: Network diagram for health-related quality of life

Table 4.44: Staircase diagram for health-related quality of life

PBO	**PBO**		
ALED10	-0.07 (-8.92, 8.75)	**ALED10**	
ZOLY5	0.08 (-6.20, 6.42)	0.08 (-6.20, 6.42)	**ZOLY5**

PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ZOLY5=zoledronic acid 5 mg/year.

4.3.10 WITHDRAWAL DUE TO ADVERSE EVENTS

A total of 35 studies and 21 treatments were included in the network investigating odds of withdrawals due to adverse events (total 26490 participants) (84, 85, 91, 95-97, 121, 124, 125, 133-135, 137, 138, 143, 144, 146, 147, 150, 153-157, 159, 160, 163, 165-167, 172-177). Ten studies were classified as primary prevention, and 25 were secondary studies. Of the two-arm studies, 22 were placebo-controlled and 7 were head-to-head studies. Among three-arm studies, four had placebo controls and two had head-to-head comparisons only. Publication years ranged from 1990 to 2015, and treatment duration ranged from 48 weeks to 5 years. No treatment appears significantly better than any comparator at reducing withdrawal due to adverse events. However, oral pamidronate 150 mg/day appears to be significantly worse than placebo (OR 5.98, 95% CrI: 1.51, 44.82) and many other treatments. No pattern was found in association with frequency (*e.g.,* daily, monthly, or yearly) or route of administration (*e.g.,* intravenous, oral, or intramuscular).

Figure 4.21: Network diagram for withdrawal due to adverse events

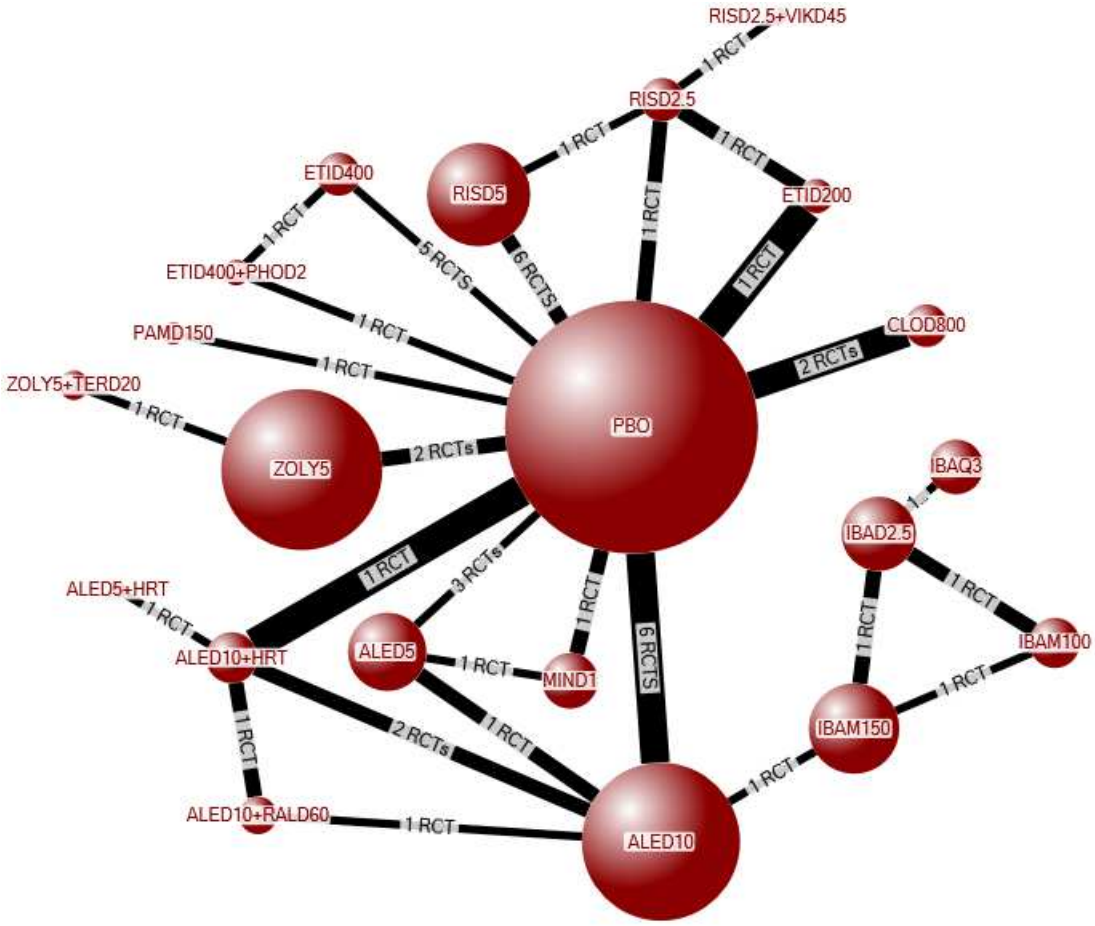


Table 4.45: Staircase diagram of withdrawal due to adverse events

	PBO	ALED5	ALED5 +HRT	ALED10	ALED10 +HRT	ALED10 +RALD60	ETID200	ETID400	ETID400 +PHOD2	RISD2.5	RISD2.5 +VIKD45	RISD5	IBAD2.5	IBAM100	IBAM150	IBAQ3	ZOLY5	ZOLY5 +TERD20	MIND1	CLOD800	PAMD150
PBO	**PBO**																				
ALED5	1.34 (0.82,2.10)	**ALED5**																			
ALED5 +HRT	1.31 (0.20,7.77)	0.98 (0.15,6.23)	**ALED5 +HRT**																		
ALED10	0.98 (0.70,1.32)	0.73 (0.43,1.27)	0.74 (0.13,4.70)	**ALED10**																	
ALED10 +HRT	1.79 (0.87,3.62)	1.34 (0.59,3.15)	1.35 (0.26,7.56)	1.83 (0.93,3.58)	**ALED10 +HRT**																
ALED10 +RALD60	0.80 (0.27,2.24)	0.60 (0.19,1.84)	0.60 (0.09,4.23)	0.82 (0.29,2.23)	0.45 (0.16,1.14)	**ALED10 +RALD60**															
ETID200	1.48 (0.45,5.01)	1.12 (0.30,4.12)	1.12 (0.12,10.46)	1.51 (0.44,5.25)	0.82 (0.20,3.44)	1.85 (0.37,9.45)	**ETID200**														
ETID400	1.37 (0.64,3.03)	1.03 (0.42,2.65)	1.05 (0.15,8.13)	1.40 (0.62,3.38)	0.76 (0.28,2.26)	1.71 (0.49,6.29)	0.92 (0.23,4.14)	**ETID400**													
ETID400 +PHOD2	0.31 (0.01,2.55)	0.24 (0.01,2.04)	0.24 (0.01,3.97)	0.32 (0.01,2.71)	0.18 (0.01,1.62)	0.40 (0.01,4.26)	0.22 (0.01,2.35)	0.23 (0.01,1.82)	**ETID400 +PHOD2**												
RISD2.5	1.56 (0.68,3.73)	1.16 (0.46,3.19)	1.18 (0.17,9.91)	1.59 (0.66,3.99)	0.88 (0.28,2.69)	1.96 (0.49,7.86)	1.08 (0.36,2.91)	1.15 (0.35,3.46)	5.05 (0.46,135.00)	**RISD2.5**											
RISD2.5 +VIKD45	2.78 (0.73,10.89)	2.08 (0.50,8.77)	2.09 (0.23,21.48)	2.84 (0.72,11.64)	1.55 (0.33,7.23)	3.51 (0.59,19.09)	1.88 (0.41,8.44)	2.04 (0.41,9.36)	8.96 (0.64,280.60)	1.77 (0.60,5.24)	**RISD2.5 +VIKD45**										
RISD5	0.89 (0.66,1.18)	0.66 (0.38,1.17)	0.67 (0.11,4.54)	0.90 (0.59,1.42)	0.49 (0.23,1.09)	1.11 (0.38,3.40)	0.60 (0.18,2.02)	0.65 (0.27,1.47)	2.82 (0.33,74.81)	0.57 (0.24,1.31)	0.32 (0.08,1.20)	**RISD5**									
IBAD2.5	1.11 (0.45,2.68)	0.83 (0.31,2.32)	0.84 (0.11,6.04)	1.14 (0.49,2.65)	0.63 (0.21,1.81)	1.40 (0.37,5.28)	0.76 (0.17,3.30)	0.81 (0.24,2.68)	3.55 (0.37,85.96)	0.72 (0.20,2.39)	0.40 (0.07,1.99)	1.26 (0.49,3.15)	**IBAD2.5**								
IBAM100	1.22 (0.49,2.91)	0.91 (0.33,2.48)	0.91 (0.12,6.73)	1.25 (0.52,2.86)	0.68 (0.23,1.97)	1.52 (0.41,5.76)	0.84 (0.18,3.59)	0.89 (0.25,2.97)	3.82 (0.39,102.10)	0.79 (0.22,2.61)	0.44 (0.08,2.21)	1.37 (0.52,3.47)	1.09 (0.58,2.01)	**IBAM100**							
IBAM150	1.00 (0.51,1.91)	0.75 (0.34,1.68)	0.76 (0.12,5.02)	1.02 (0.57,1.84)	0.56 (0.23,1.35)	1.25 (0.39,4.13)	0.68 (0.17,2.63)	0.73 (0.25,2.00)	3.18 (0.35,81.44)	0.65 (0.21,1.81)	0.36 (0.08,1.62)	1.13 (0.54,2.28)	0.90 (0.48,1.67)	0.82 (0.44,1.53)	**IBAM150**						
IBAQ3	1.29 (0.45,3.73)	0.97 (0.32,3.17)	0.97 (0.12,7.98)	1.33 (0.49,3.75)	0.73 (0.22,2.47)	1.63 (0.39,7.00)	0.89 (0.17,4.42)	0.95 (0.25,3.64)	4.15 (0.39,109.30)	0.85 (0.21,3.20)	0.47 (0.08,2.70)	1.47 (0.49,4.41)	1.17 (0.65,2.11)	1.07 (0.47,2.51)	1.29 (0.58,3.08)	**IBAQ3**					
ZOLY5	1.14 (0.67,1.89)	0.85 (0.43,1.73)	0.86 (0.14,5.97)	1.17 (0.64,2.14)	0.64 (0.27,1.53)	1.42 (0.45,4.56)	0.78 (0.20,2.82)	0.83 (0.32,2.07)	3.61 (0.42,96.55)	0.74 (0.26,1.96)	0.41 (0.10,1.80)	1.29 (0.71,2.33)	1.02 (0.37,2.84)	0.93 (0.34,2.64)	1.14 (0.51,2.62)	0.87 (0.27,2.72)	**ZOLY5**				
ZOLY5 +TERD20	2.94 (0.49,22.26)	2.18 (0.35,18.19)	2.31 (0.18,32.78)	3.01 (0.50,23.22)	1.67 (0.25,13.86)	3.75 (0.46,37.83)	2.00 (0.25,20.68)	2.17 (0.30,20.46)	9.84 (0.57,349.80)	1.88 (0.27,17.43)	1.06 (0.11,13.39)	3.31 (0.55,25.21)	2.66 (0.38,21.74)	2.46 (0.35,20.62)	2.95 (0.46,22.95)	2.29 (0.30,19.59)	2.59 (0.47,18.62)	**ZOLY5 +TERD20**			
MIND1	1.26 (0.75,2.15)	0.94 (0.52,1.84)	0.96 (0.16,6.74)	1.29 (0.72,2.42)	0.71 (0.30,1.71)	1.58 (0.51,5.23)	0.86 (0.23,3.22)	0.92 (0.36,2.42)	4.02 (0.48,106.90)	0.82 (0.29,2.20)	0.46 (0.10,1.94)	1.43 (0.78,2.63)	1.13 (0.41,3.24)	1.04 (0.38,3.02)	1.26 (0.55,3.00)	0.97 (0.30,3.24)	1.11 (0.54,2.39)	0.43 (0.05,2.78)	**MIND1**		
CLOD800	1.55 (0.85,2.80)	1.16 (0.55,2.49)	1.18 (0.18,8.59)	1.58 (0.81,3.11)	0.86 (0.34,2.27)	1.92 (0.60,6.81)	1.04 (0.26,4.09)	1.13 (0.42,3.00)	4.92 (0.55,134.80)	1.00 (0.34,2.75)	0.56 (0.13,2.43)	1.75 (0.90,3.37)	1.38 (0.49,4.06)	1.26 (0.44,3.76)	1.54 (0.65,3.77)	1.19 (0.35,3.98)	1.36 (0.61,3.03)	0.53 (0.06,3.48)	1.23 (0.55,2.68)	**CLOD800**	
PAMD150	**5.98 (1.51,44.82)**	**4.49 (1.07,34.80)**	4.78 (0.49,74.16)	**6.14 (1.53,47.47)**	3.41 (0.71,26.58)	**7.64 (1.33,74.49)**	4.14 (0.67,47.08)	4.37 (0.92,36.02)	**19.43 (1.46,1115)**	3.91 (0.74,35.87)	2.22 (0.32,23.86)	6.74 (1.64,51.65)	**5.34 (1.07,45.90)**	4.99 (0.97,41.47)	**6.02 (1.35,46.96)**	4.61 (0.82,42.97)	**5.21 (1.24,41.03)**	2.10 (0.20,25.96)	**4.75 (1.10,37.02)**	3.84 (0.88,31.13)	**PAMD150**

Red cells with white bolded font indicate significant harmful effect.PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, VIKD45=vitamin K 45 mg/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year, TERD20=teriparatide 20 µg/day, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, PAMD150=pamidronate 150 mg/day.

4.3.11 SEROUS ADVERSE EVENTS

The network meta-analysis included 27 studies and 14 treatments representing 34452 participants (82, 84, 90, 91, 95, 97, 117, 124, 125, 131, 133, 137, 143, 144, 150, 154-160, 162, 163, 165, 167, 173). Eight studies are primary prevention trials, and 19 are secondary prevention trials. The studies were published from 1995 to 2014 with one to five years in duration. Of the 20 two-arm treatments, 16 are placebo-controlled, and 4 are head-to-head comparisons. Of the 7 three-arm trials, 5 have placebo comparisons and the rest have only head-to-head comparisons. Most trials compared placebo to alendronate 10 mg/day (12 studies) and to risedronate 5 mg/day (7 studies). No treatment was associated with significant reductions in odds of serious adverse events compared to placebo or to each other.

Figure 4.22: Network diagram for serious adverse events

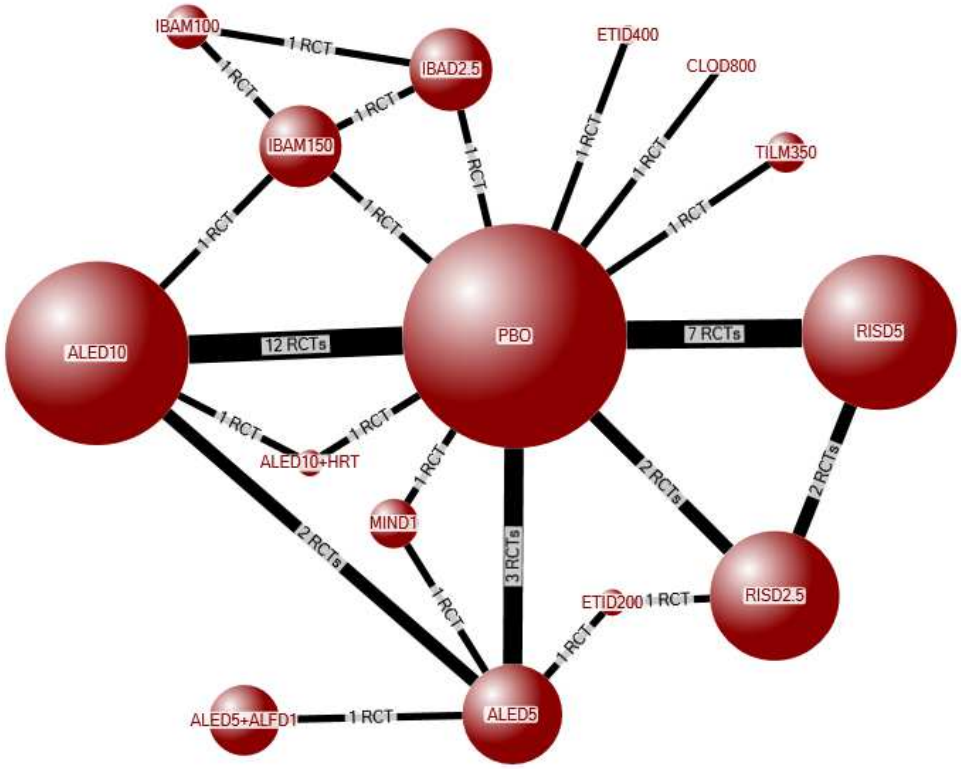


Table 4.46: Staircase diagram of serious adverse events

PBO	**PBO**													
ALED5	0.90 (0.68,1.20)	**ALED5**												
ALED10	1.12 (0.86,1.45)	1.24 (0.87,1.76)	**ALED10**											
ALED10+HRT	1.19 (0.61,2.52)	1.33 (0.65,2.92)	1.08 (0.55,2.20)	**ALED10 +HRT**										
ALED10 +RALD60	1.60 (0.13,18.55)	1.77 (0.14,20.76)	1.46 (0.12,15.64)	1.33 (0.11,12.87)	**ALED10 +RALD60**									
ETID400	0.75 (0.36,1.48)	0.83 (0.39,1.76)	0.67 (0.31,1.37)	0.62 (0.23,1.66)	0.46 (0.03,6.06)	**ETID400**								
RISD2.5	0.98 (0.74,1.24)	1.08 (0.73,1.57)	0.88 (0.59,1.23)	0.82 (0.37,1.65)	0.61 (0.05,7.45)	1.30 (0.62,2.75)	**RISD2.5**							
RISD5	1.01 (0.85,1.20)	1.12 (0.80,1.57)	0.91 (0.66,1.24)	0.85 (0.39,1.70)	0.63 (0.05,7.85)	1.35 (0.66,2.81)	1.04 (0.82,1.37)	**RISD5**						
IBAD2.5	1.05 (0.75,1.41)	1.16 (0.76,1.73)	0.94 (0.63,1.34)	0.88 (0.38,1.81)	0.65 (0.06,7.72)	1.40 (0.65,3.02)	1.07 (0.71,1.61)	1.04 (0.71,1.46)	**IBAD2.5**					
IBAM100	1.42 (0.83,2.38)	1.57 (0.85,2.81)	1.27 (0.73,2.11)	1.18 (0.49,2.73)	0.87 (0.07,11.27)	1.88 (0.78,4.71)	1.45 (0.81,2.61)	1.40 (0.80,2.41)	1.35 (0.85,2.17)	**IBAM100**				
IBAM150	1.01 (0.67,1.51)	1.12 (0.68,1.81)	0.90 (0.61,1.32)	0.84 (0.37,1.78)	0.62 (0.05,7.91)	1.33 (0.61,3.17)	1.03 (0.65,1.70)	0.99 (0.64,1.56)	0.96 (0.64,1.46)	0.71 (0.44,1.16)	**IBAM150**			
IBAQ3	0.94 (0.53,1.62)	1.04 (0.55,1.92)	0.85 (0.46,1.51)	0.79 (0.31,1.83)	0.59 (0.05,7.30)	1.26 (0.52,3.10)	0.97 (0.52,1.78)	0.93 (0.51,1.65)	0.90 (0.57,1.43)	0.67 (0.35,1.29)	0.94 (0.50,1.73)	**IBAQ3**		
ZOLY5	0.97 (0.76,1.25)	1.08 (0.74,1.56)	0.87 (0.63,1.20)	0.81 (0.37,1.65)	0.60 (0.05,7.46)	1.30 (0.63,2.75)	0.99 (0.71,1.47)	0.96 (0.71,1.32)	0.93 (0.64,1.40)	0.68 (0.39,1.24)	0.96 (0.61,1.55)	1.03 (0.57,1.92)	**ZOLY5**	
MIND1	0.75 (0.48,1.20)	0.83 (0.50,1.42)	0.67 (0.40,1.12)	0.62 (0.27,1.41)	0.46 (0.04,5.77)	1.00 (0.45,2.33)	0.77 (0.47,1.33)	0.74 (0.46,1.22)	0.72 (0.42,1.28)	0.53 (0.27,1.07)	0.75 (0.41,1.38)	0.80 (0.39,1.69)	0.77 (0.47,1.31)	**MIND1**

PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, RALD60=raloxifene 60 mg/day, ETID400=etidronate 400 mg/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year.

4.3.12 GASTROINTESTINAL ADVERSE EVENTS

The network for gastrointestinal adverse events included 32 studies (total 34803 participants) with 15 orally administered treatments (82, 85-88, 90, 91, 93, 95, 96, 117, 120, 121, 124, 133, 137, 141, 144, 146, 150, 155, 156, 158, 159, 161, 162, 165, 167, 168, 172, 173, 178). Eight are primary prevention studies, and 24 are secondary studies. Publication ranged from 1995 to 2011, and study durations from 48 weeks to five years. Of these studies, 19 are two-arm placebo-controlled studies, 5 are two-arm head-to-head comparisons, 7 studies are three-arm placebo-controlled studies, and 1 is a three-arm head-to-head study. Oral etidronate 400 mg/day is associated with a significant 82% reduction in odds of gastrointestinal adverse events compared to oral clodronate 800 mg/day (OR 0.18, 95% CrI: 0.04,0.76) and a significant 69% reduction compared to oral alendronate 10 mg/day with hormone replacement therapy (OR 0.31, 95% CrI: 0.10, 0.92). No other significant comparisons were found.

Figure 4.23: Network diagram for gastrointestinal adverse events

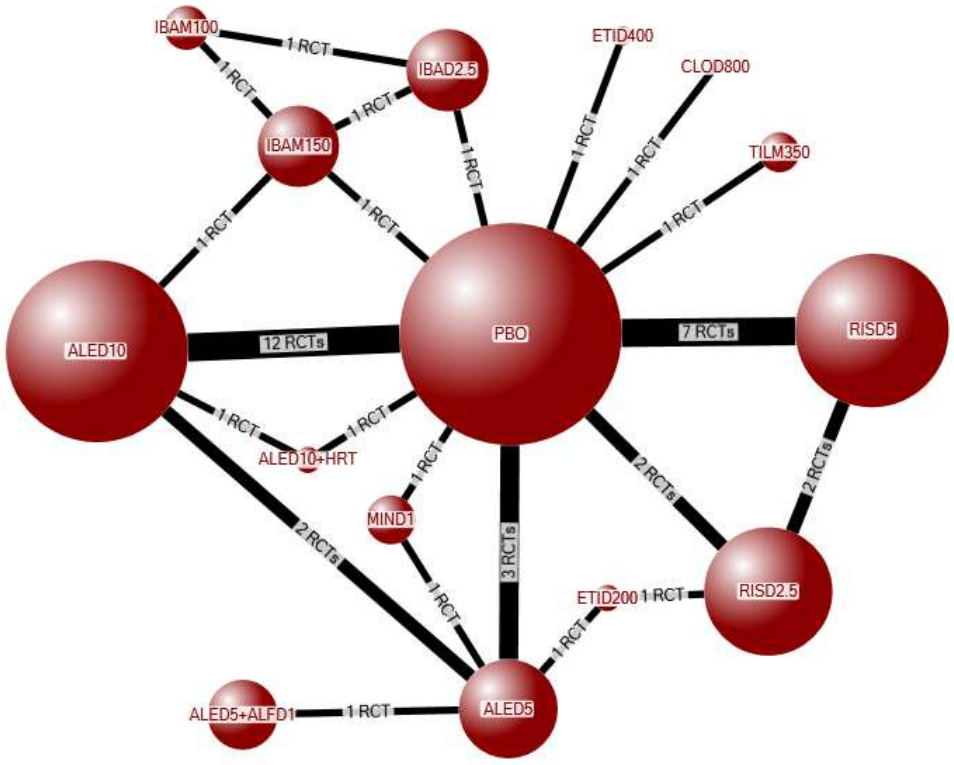


Table 4.47: Staircase diagram for gastrointestinal adverse events

PBO	**PBO**														
ALED5	0.93 (0.75,1.15)	**ALED5**													
ALED5 +ALFD1	0.93 (0.63,1.34)	0.99 (0.73,1.34)	**ALED5 +ALFD1**												
ALED10	1.03 (0.93,1.14)	1.10 (0.88,1.39)	1.11 (0.76,1.64)	**ALED10**											
ALED10 +HRT	1.51 (0.88,2.58)	1.62 (0.92,2.88)	1.64 (0.85,3.15)	1.47 (0.87,2.51)	**ALED10 +HRT**										
ETID200	0.95 (0.52,1.90)	1.02 (0.53,2.13)	1.03 (0.50,2.24)	0.93 (0.50,1.86)	0.64 (0.28,1.49)	**ETID200**									
ETID400	0.46 (0.18,1.16)	0.50 (0.19,1.27)	0.50 (0.18,1.34)	0.45 (0.17,1.13)	**0.31 (0.10,0.92)**	0.48 (0.15,1.58)	**ETID400**								
RISD2.5	1.07 (0.90,1.30)	1.15 (0.87,1.54)	1.16 (0.78,1.78)	1.04 (0.85,1.29)	0.71 (0.40,1.25)	1.12 (0.58,2.04)	2.33 (0.90,6.11)	**RISD2.5**							
RISD5	1.01 (0.89,1.16)	1.09 (0.84,1.40)	1.10 (0.74,1.65)	0.99 (0.83,1.17)	0.67 (0.39,1.17)	1.06 (0.54,1.98)	2.20 (0.87,5.78)	0.95 (0.78,1.13)	**RISD5**						
IBAD2.5	0.95 (0.76,1.21)	1.02 (0.75,1.41)	1.03 (0.68,1.62)	0.93 (0.73,1.19)	0.63 (0.36,1.12)	1.00 (0.49,1.94)	2.06 (0.77,5.54)	0.89 (0.66,1.20)	0.94 (0.72,1.24)	**IBAD2.5**					
IBAM100	1.20 (0.85,1.73)	1.28 (0.86,1.98)	1.29 (0.79,2.21)	1.16 (0.82,1.69)	0.79 (0.42,1.52)	1.25 (0.58,2.54)	2.59 (0.95,7.30)	1.12 (0.75,1.69)	1.18 (0.81,1.75)	1.25 (0.90,1.77)	**IBAM100**				
IBAM150	1.07 (0.85,1.36)	1.14 (0.85,1.59)	1.16 (0.76,1.82)	1.04 (0.84,1.31)	0.71 (0.40,1.26)	1.12 (0.54,2.16)	2.32 (0.90,6.21)	1.00 (0.75,1.35)	1.06 (0.81,1.39)	1.12 (0.86,1.46)	0.90 (0.63,1.25)	**IBAM150**			
MIND1	1.12 (0.83,1.49)	1.19 (0.86,1.66)	1.20 (0.77,1.89)	1.09 (0.79,1.48)	0.73 (0.40,1.33)	1.17 (0.55,2.28)	2.41 (0.89,6.70)	1.04 (0.73,1.46)	1.10 (0.79,1.51)	1.17 (0.80,1.68)	0.93 (0.58,1.46)	1.04 (0.71,1.49)	**MIND1**		
CLOD800	2.57 (0.78,8.09)	2.74 (0.84,8.86)	2.76 (0.84,9.29)	2.50 (0.76,7.84)	1.69 (0.46,6.14)	2.70 (0.69,10.31)	**5.53 (1.31,24.58)**	2.39 (0.72,7.74)	2.53 (0.76,8.11)	2.67 (0.80,8.51)	2.14 (0.63,7.11)	2.40 (0.72,7.61)	2.29 (0.69,7.45)	**CLOD800**	
TILM350	0.87 (0.59,1.32)	0.94 (0.59,1.52)	0.94 (0.54,1.68)	0.85 (0.56,1.30)	0.58 (0.29,1.13)	0.91 (0.42,1.92)	1.89 (0.69,5.47)	0.82 (0.52,1.27)	0.86 (0.56,1.33)	0.92 (0.58,1.46)	0.73 (0.42,1.26)	0.81 (0.51,1.30)	0.79 (0.48,1.31)	0.34 (0.10,1.20)	**TILM350**

Green cells with bolded black font indicate significant preventive effect, red cells with white bolded font indicate significant harmful effect. PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5=ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, TILM350=tiludronate 350 mg/month.

4.3.13 ACUTE PHASE RESPONSE

Six studies were included in the network meta-analysis for acute phase response among five intravenously administered treatments (total 8595 participants) (125, 128, 131, 132, 149, 179). Five studies were two-arm, placebo-controlled studies, and one study had a placebo arm as well as three monthly neridronate doses: 12.5 mg, 25 mg, and 50 mg. Intravenous zoledronic acid 5 mg/year was assessed in three studies against placebo, and neridronate 25 mg/month was assessed in three trials. The results showed patients receiving zoledronic acid 5 mg/year (OR 3.69, 95% CrI: 1.16, 11.59) and neridronate 25 mg/month (OR 8.82, 95% CrI: 2.04, 44.32) had significantly higher likelihood of acute phase response compared to those receiving placebo. Neridronate 25 mg/month is associated with a non-significant 4% reduction in odds of acute phase response compared to zoledronic acid 5 mg/year (OR 0.96, 95% CrI: 0.08, 10.44).

Figure 4.24: Network diagram for acute phase response

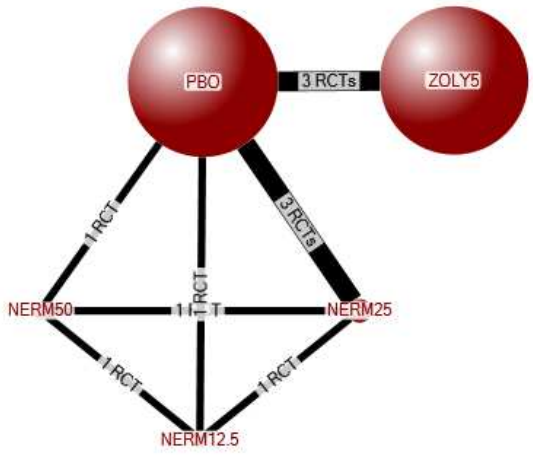


Table 4.48: Staircase diagram for acute phase response

PBO	**PBO**				
ZOLY5	**3.69 (1.16,11.59)**	**ZOLY5**			
NERM12.5	3.55 (0.40,28.88)	0.96 (0.08,10.44)	**NERM12.5**		
NERM25	**8.82 (2.04,44.32)**	2.38 (0.38,17.54)	2.50 (0.36,22.01)	**NERM25**	
NERM50	5.22 (0.62,40.04)	1.42 (0.12,14.47)	1.48 (0.16,13.29)	0.59 (0.07,3.95)	**NERM50**

Red cells with white bolded font indicate significant harmful effect.PBO=placebo, ZOLY5=zoledronic acid 5 mg/year, NERM12.5=neridronate 12.5 mg/month, NERM25=neridronate 25 mg/month, NERM50=neridronate 50 mg/month.

4.3.14 OSTEONECROSIS OF THE JAW

A network MA was not conducted for osteonecrosis of the jaw. Twenty studies reported the outcome (total 21073 participants); however, only two studies reported non-zero events. One study reported a case in the risedronate 5 mg/day treatment group after one year of treatment, where a patient was "hospitalized for partial necrosis of the left mandible after a tooth extraction" (180). However, this data could not be included in the network because both treatment groups (*i.e.,* risedronate weekly 35 mg and daily 5 mg) had the same total dose, and would be combined as one arm in analysis. In the HORIZON trial, a retrospective search of the safety database with expert adjudication found two cases of "potential necrosis of the jaw", one each in the placebo and zoledronic acid group. In the first three-year extension of HORIZON where participants have a total of four to six years of treatment with zoledronic acid, one case was found in the zoledronic acid group meeting the criteria for jaw osteonecrosis.

4.3.15 ATYPICAL FEMORAL FRACTURE

No network meta-analysis was conducted for atypical femoral fracture. Of 35 studies that reported the outcome (total 15638 participants), only the HORIZON study reported non-zero events: two cases in the placebo group and three cases in the zoledronic acid group (7765 randomized; 7714 in analysis). The definition used for adjudication was “a diaphyseal fracture below the lesser trochanter and above the distal metaphysis” (125).

4.3.16 ATRIAL FIBRILLATION

No network was conducted for atrial fibrillation, but the outcome was reported in 12 studies (total 14016 participants). Only the HORIZON trial and two other studies reported non-zero data (181, 182). The first study included risedronate 5 mg/day and a monthly 150 mg dose, where more women taking the monthly dose had atrial fibrillation (7/650, 1.1%) compared the daily dose (4/642, 0.6%) (181). The second study included risedronate 5 mg/day and 35 mg/week (182), where more women taking the weekly dose (2/615, 0.3%) had atrial fibrillation compared to the daily dose (0/307, 0%). However, since both studies had total equivalent doses, they each became a one-arm study after dose pooling and were excluded from analysis. The HORIZON trial showed greater rate of atrial fibrillation among participants in the zoledronic acid 5 mg/year group (73/3852, 2.4%) compared to the control group (94/3862, 1.9%).

4.4 DISCUSSION

4.4.1 SUMMARY OF RESULTS

We conducted a comprehensive network meta-analysis of the harms and benefits of bisphosphonates alone and in combination for osteoporosis in postmenopausal women. We included 83 studies in the network meta-analyses examining 10 outcomes. In each domain assessed for risk of bias, there were more studies in the low risk of bias category compared to high risk. Few studies were primary prevention trials (15/83, 18%). Thus, subgroup analyses of primary prevention trials were not possible for radiographic vertebral fractures and hip fractures. No statistically significant comparisons were found for primary prevention subgroup analyses on the remaining efficacy outcomes.

Ten interventions were superior to placebo for preventing radiographic vertebral fractures: alendronate 5 and 10 mg/day, etidronate 200 and 400 mg/day, risedronate 5 mg/day, ibandronate 2.5 mg/day, zoledronic acid 5 mg/year, minodronate 1 mg/day, etidronate 400 mg/day with hormone replacement therapy, and etidronate 400 mg/day with phosphate 2 g/day. All ten comparisons remained significant among secondary prevention studies. Only alendronate 10 mg/day and minodronate were consistently superior to placebo among bisphosphonate-naïve participants and when treatment durations were separated by year and evaluated individually. Although not statistically significant in the main analysis, alendronate with raloxifene 60 mg/day showed greater efficacy than placebo among secondary studies and studies with low risk of bias. Zoledronic acid was superior to alendronate 10 mg/day in the main and secondary prevention analyses, risedronate 5 mg/day in the main and three years treatment analyses, clodronate 800 mg/day in the main, secondary prevention, one year treatment, and three years treatment analyses, and monthly tiludronate (350 mg, 1400 mg) in the main, secondary, one year and three year analyses.

Only alendronate 10 mg/day (OR 0.44, 95% CrI: 0.26, 0.72) and zoledronic acid 5 mg/year (OR 0.22, 95% CrI: 0.10, 0.44) were superior to placebo for preventing clinical vertebral fractures in the main analysis, among secondary studies, bisphosphonate-naïve studies, low risk of bias studies, trials

with five main bisphosphonates, and among three year treatment durations. Among trials with two years of treatment, alendronate lost significance and zoledronic acid was not evaluated. Among studies with fracture as an efficacy outcome, zoledronic acid remained significant while alendronate lost statistical significance. Zoledronic acid was superior to risedronate (2.5 mg, 5 mg) for reducing clinical vertebral fractures in the main analysis and among trials with one of the five main bisphosphonates (OR 0.21, 95% CrI: 0.06, 0.71; OR 0.23, 95% CrI: 0.06, 0.86)

Non-vertebral fractures were supported by the largest number of studies. Only alendronate 10 mg/day was significantly better than placebo in the main analysis (OR 0.78, 95% CrI: 0.60, 0.98), and this result persisted when only secondary studies, trials with low risk of bias, studies with one of five main bisphosphonates, and trials with two years of treatment were assessed. No treatment was significant better than any comparator among primary studies, trials with bisphosphonate naïve participants, trials with bisphosphonate-experienced participants, or studies with fracture as efficacy outcome. Risedronate 2.5 mg/day and 5 mg/day were significant better than placebo only in the network with one year treatment data. Zoledronic acid with teriparatide was superior to alendronate 5 mg/day only in the network of studies with low risk of bias.

Zoledronic acid is the only treatment that showed a significant reduction in hip fracture (compared to placebo, OR 0.55, 95% CrI: 0.34, 0.85), and the result was consistent across networks of secondary studies and trials with fracture as an efficacy outcome. Alendronate 10 mg/day was significantly better than placebo only among secondary prevention trials, and trials with bisphosphonate-naïve participants. No significant results were found when trials were broken down by treatment duration and risk of bias.

Wrist fractures were supported by the fewest studies at nine trials. No treatment was significantly better than any comparator in the main analysis or any of the subgroup and sensitivity analyses, except for zoledronic acid which was significant better than placebo only among secondary prevention studies (OR 0.17, 95% CrI: 0.02, 0.96).

Health-related quality of life was analyzed in two trials and did not show any significant differences among placebo, alendronate 10 mg/day, or zoledronic acid 5 mg/year. No treatment was significantly better than any comparator for reducing odds of withdrawal due to adverse events, however, pamidronate 150 mg/day is associated with an increase in events compared to placebo (OR 5.98, 95% CrI: 1.51, 44.82) and other bisphosphonates. Serious adverse events were not significantly different between treatments. Lower odds of gastrointestinal events were found for etidronate 400 mg/day compared to clodronate 800 mg/day (OR 0.18, 95% CrI: 0.04, 0.76) and alendronate 10 mg/day combined with HRT (OR 0.31, 95% CrI: 0.10, 0.92). Higher odds of acute phase response were found in patients taking yearly zoledronic acid (OR 3.69, 95% CrI: 1.16, 11.59) and monthly neridronate 25 mg (OR 8.82, 95% CrI: 2.04, 44.32) compared to placebo. No network was done for rare adverse events due to a lack of studies providing non-zero data.

The longest duration of treatment was five years, which was reported by two extension studies, FLEX and VERT, for the outcomes radiographic vertebral and non-vertebral fracture (87, 144). Individual trial results showed lower fracture rates in alendronate (FLEX) and risedronate (VERT) groups. However, pooled findings did not show significant differences from placebo in fracture prevention.

Most combination treatments did not show greater significance than the treatment administered alone. No difference in efficacy was observed among the 200 mg versus 400 mg doses of etidronate or among 2.5 mg versus 5 mg doses of risedronate. However, a daily 10 mg dose of alendronate is more efficacious than the 5 mg dose. The 10 mg dose showed significant results for prevention of both types of vertebral fractures and non-vertebral fractures compared to placebo, while the 5 mg dose is only significantly better than placebo at preventing radiographic vertebral fracture.

We evaluated the assumptions of exchangeability, homogeneity, and consistency underlying network meta-analysis. Exchangeability is fulfilled when there is sufficient similarity between all included trials in the analysis in terms of methodological and clinical characteristics (183). Homogeneity assumes that there is adequate similarity between trials at the level of pairwise

comparisons for any two interventions supported by direct evidence. Both of these assumptions were evaluated by comparing the study and participant characteristics between all included trials and trials within pairwise comparisons in Table 4.4. We did observe variation between some study characteristics, for example study duration that ranged from 48 weeks to 5 years. However, the variation was expected given the breadth of our eligibility criteria which did not restrict the maximum length of the trial, and given our research question which aimed to assess long-term use of bisphosphonates greater than one year duration. Additionally, for the pairwise comparison of alendronate versus placebo, Tables 4.49 and 4.50 compare the estimates based on direct evidence from the systematic review conducted in Chapter 3 to results from the network meta-analysis based on direct and indirect evidence conducted in Chapter 4, and with results from the Cochrane review conducted in 2008. The first column presents results from the Cochrane review, which combined radiographic and clinical vertebral fractures as one outcome. The second column of the table shows results of the systematic review in Chapter 3 as relative risk, and the last two columns present results of the network meta-analysis as odds ratios (the original effect estimate generated by the software) and relative risk converted from odds ratios. We observed a high degree of similarity between the Cochrane review estimates and the results from the review conducted in Chapter 3. Relative risk estimates from the systematic review are identical to estimates from the network meta-analysis for clinical vertebral fractures and wrist fractures (clinical vertebral RR 0.45, wrist RR 0.82). The greatest variability between the relative risk estimates occurred in hip fractures with a 7% difference in risk reduction (review RR 0.61, NMA RR 0.68). This may be attributed to a different number of included trials in the comparison of the systematic review which allowed active comparators and the network meta-analysis which only included placebo or bisphosphonate comparators. Overall we did not observe any substantial deviations from the homogeneity or exchangeability assumptions based on qualitative comparisons of characteristics. Finally, the assumption of consistency is met if data from direct comparisons are similar to evidence from indirect comparisons and the consistency equations hold (184). The assumption was assessed using the inconsistency model method within each closed loop for which there is both direct and

indirect evidence. We found that radiographic vertebral fracture, non-vertebral fracture and wrist fracture showed evidence of inconsistency based on the plotting of residual deviances from inconsistency and consistency models. Potential reasons for inconsistency are explored in Appendix 8, and sensitivity analyses excluding the inconsistent study were conducted. We observed no substantial changes in effect estimates from the main analysis in the sensitivity analyses. Thus, in order to provide a representative view of the available studies in the literature that met our eligibility criteria, results of the main analysis were presented for each NMA.

Table 4.49: Results of systematic reviews and NMA for alendronate 10 mg/day versus placebo

Site of fracture	Cochrane review RR (95% CI)	Systematic review (Chapter 3) RR (95% CI)	Network MA (Chapter 4) RR (95% CrI)	Network MA (Chapter 4) OR (95% CrI)
Radio. vertebral	**0.55 (0.45, 0.67)***	**0.55 (0.45, 0.67)**	**0.61 (0.48,0.78)**	**0.58 (0.44,0.76)**
Clinical vertebral		**0.45 (0.28, 0.73)**	**0.45 (0.27,0.73)**	**0.44 (0.26, 0.72)**
Non-vertebral	**0.84 (0.74, 0.94)**	**0.83 (0.73, 0.93)**	**0.79 (0.62,0.98)**	**0.78 (0.60,0.98)**
Hip	**0.61 (0.40, 0.92)**	**0.61 (0.40, 0.93)**	0.68 (0.45,1.00)	0.68 (0.44,1.00)
Wrist	0.68 (0.34, 1.37)	0.82 (0.44, 1.54)	0.82 (0.45,1.48)	0.81 (0.44,1.49)

Bolded results indicate significance. *Both types of vertebral fracture were combined in the Cochrane review in 2008.

Table 4.50: Results of systematic reviews and NMA for alendronate 5 mg/day versus placebo

Site of fracture	Cochrane review RR (95% CI)	Systematic review (Chapter 3) RR (95% CI)	NMA (Chapter 4) RR (95% CrI)	NMA (Chapter 4) OR (95% CrI)
Radio. vertebral	**0.40 (0.29, 0.55)***	**0.56 (0.35, 0.90)**	**0.57 (0.34,0.93)**	**0.54 (0.31,0.93)**
Clinical vertebral		1.02 (0.06, 16.10)	0.97 (0.07,8.31)	0.97 (0.07,10.69)
Non-vertebral	0.95 (0.34, 2.67)	0.81 (0.45, 1.46)	0.79 (0.62,0.98)	0.86 (0.54,1.37)
Hip	--	0.40 (0.02, 8.21)	--	--
Wrist	--	--	--	--

Dashed lines indicate results were not estimable due to lack of study data. Bolded results indicate significance. *Both types of vertebral fracture were combined in the Cochrane review published in 2008.

4.4.2 COMPARISON TO LITERATURE

Globally, alendronate 10 mg/day and zoledronic acid appear effective for preventing the most types of fractures. Many treatments showed efficacy for radiographic vertebral fractures while only alendronate or zoledronic acid showed efficacy in non-vertebral sites. However, more studies assessed alendronate than any other bisphosphonate. Overall, NMA results are consistent with direct evidence from the systematic review on alendronate in Chapter 3 and previously conducted Cochrane reviews on alendronate, etidronate, and risedronate. Tables 4.49 to 4.52 summarize

findings from the previous Cochrane reviews (32-34), the systematic review in Chapter 3, and the network meta-analyses from Chapter 4 with estimates provided as odds ratios and risk ratios, respectively. Vertebral fractures from Cochrane reviews are divided into radiographic and clinical fractures in the analyses from Chapters 3 and 4. Findings also align with recommendations of clinical practice guidelines suggesting postmenopausal women at risk of fracture to begin with oral alendronate treatment and for high-risk populations to receive zoledronic acid. Ibandronate and etidronate are recommended primarily for prevention of spinal fracture which is consistent with results of the current analysis. Additionally, we found minodronate showed greater efficacy than placebo for vertebral fracture prevention. Clodronate, tiludronate and pamidronate did not show greater efficacy than any other comparator.

Table 4.51: Results of systematic review and NMA for daily risedronate 5 mg or 2.5 mg versus placebo

Site of fracture	Risedronate 5 mg/day			Risedronate 2.5 mg/day		
	Cochrane MA RR (95% CI)	Network MA RR (95% CrI)	Network MA OR (95% CrI)	Cochrane MA RR (95% CI)	Network MA RR (95% CrI)	Network MA OR (95% CrI)
Radio. vertebral	**0.63 (0.51, 0.77)**	**0.56 (0.41,0.76)**	**0.53 (0.38,0.73)**	**0.62 (0.46, 0.83)***	0.78 (0.32,1.46)	0.75 (0.29,1.55)
Clinical vertebral		0.93 (0.33,2.63)	0.93 (0.32,2.78)		1.05 (0.40,2.87)	1.05 (0.39,3.06)
Non-vertebral	**0.80 (0.72, 0.90)**	0.84 (0.60,1.10)	0.83 (0.58,1.11)	0.50 (0.21, 1.19)	0.47 (0.13,1.44)	0.46 (0.12,1.49)
Hip	**0.74 (0.59, 0.94)**	0.73 (0.44,1.22)	0.73 (0.43,1.23)	--	--	--
Wrist	0.67 (0.42, 1.07)	0.60 (0.21,1.64)	0.59 (0.20,1.66)	--	--	--

Dashed lines indicate results were not estimable due to lack of study data. Bolded results indicate significance. *Both types of vertebral fracture were combined in the Cochrane review.

Table 4.52: Results of systematic review and NMA for daily etidronate 400 mg or 200 mg versus placebo

Site of fracture	Etidronate 400 mg/day			Etidronate 200 mg/day		
	Cochrane MA RR (95% CI)	Network MA RR (95% CrI)	Network MA OR (95% CrI)	Cochrane MA RR (95% CI)	Network MA RR (95% CrI)	Network MA OR (95% CrI)
Radio. vertebral	**0.59 (0.36, 0.96)***	**0.47 (0.23,0.90)**	**0.44 (0.21, 0.89)**	**0.32 (0.16, 0.64)***	**0.33 (0.15,0.71)**	**0.31 (0.13, 0.68)**
Clinical vertebral		--	--		--	--
Non-vertebral	0.98 (0.68, 1.42)	0.86 (0.50,1.46)	0.86 (0.49,1.50)	--	0.29 (0.05,1.10)	0.27 (0.05,1.11)
Hip	1.20 (0.37, 3.88)	0.87 (0.14,4.80)	0.87 (0.14,5.05)	0.33 (0.01, 8.04)	--	--
Wrist	0.87 (0.32, 2.36)	0.91 (0.09,7.11)	0.91 (0.09,8.04)	0.50 (0.05, 5.38)	--	--

Dashed lines indicate results were not estimable due to lack of study data. Bolded results indicate significance. *Both types of vertebral fracture were combined in the Cochrane review.

Results of other network meta-analyses assessing the efficacy of bisphosphonates for radiographic vertebral fracture prevention consistently found zoledronic acid (46, 47, 49-54), alendronate (46, 47, 49-51, 53, 54), risedronate (47, 49-51, 53, 54, 56), and ibandronate (46, 47, 49-51, 53, 54) to be significantly better than placebo. These results were also present in the current NMA. Etidronate was observed to be significantly better than placebo at preventing radiographic vertebral fractures in the current analysis, reducing the odds of fracture by 56% to 90% (depending on the dosage) compared to placebo. However, it was not significant better than placebo in three previously conducted network meta-analyses (49, 50, 54). This may be due to a smaller number of studies in other NMAs and difference in inclusion criteria. In the current analysis, seven studies were included for the etidronate node; two studies for the 200 mg/day dose and five for the 400 mg/day dose. The NMA by Zhou et al. (2016) included two studies in the etidronate node for the NMA on vertebral fractures, one of which was included in the current analysis (147) and another that was excluded from the current analysis because it included men (185). The NMA by Freemantle et al. (2012) included only Watts et al. (1990). The network by Hopkins et al. (2011) included seven studies, of which five trials overlapped with the current analysis. Two trials were not included in the current analysis because they were extracted as clinical vertebral fractures for a separate analysis (160, 163). Two studies in the current analysis were not included in the 2011 network (134, 145) which may help to explain the difference in findings.

Only the network meta-analysis by Freemantle et al. (2012) examined clinical vertebral fractures (50). The current analysis found alendronate 10 mg/day and zoledronic acid were both more effective than placebo at fracture prevention. However, although a meta-analysis by Freemantle et al. indicated alendronate 10 mg/day and zoledronic acid were both significantly better than placebo, the mixed treatment comparison was non-significant for both treatments. A reason for the discrepancy may be only six trials were included in the network by Freemantle et al. while eleven trials were included in the current analysis, thus the network may have lower power to detect potential differences between treatments.

Congruent to the current analysis, five other network meta-analyses found alendronate significantly more effective than placebo at reducing non-vertebral fractures (46, 47, 49, 54, 55). However, three of these NMAs also found zoledronic acid to be significantly better than placebo (46, 49, 54), while the odds ratio in the current analysis did not reach significance (OR 0.70, 95% CrI: 0.43, 1.13). One of the NMAs only included the HORIZON trial, which shows high efficacy for zoledronic acid compared to placebo (54). Another of the NMA included trials in men (49), and the third NMA included those with secondary osteoporosis (46), thus both had 6 studies with non-vertebral fracture that assessed zoledronic acid while there were only 3 studies in the current analysis.

In this NMA, odds of hip fracture were significantly reduced when patients received zoledronic acid, which was also reported in three other network meta-analyses (20, 52, 55). As in the current analysis, no network meta-analysis found any treatment that significantly reduced the incidence of wrist fractures. A network meta-analysis including 50 studies by Tadrous et al. in 2013 focused on safety of bisphosphonates. They found for any gastrointestinal adverse event, zoledronic acid had the highest incidence followed by etidronate and alendronate. The study NMA differed from our NMA because they included intravenous bisphosphonates like zoledronic acid for gastrointestinal events while we did not include any bisphosphonates administered intravenously for the outcome. Also, all doses of the same bisphosphonate were combined.

Most of the network meta-analyses found in literature did not examine combination treatments, and did not separate treatments by the dosage that was administered, which may help to explain some of the heterogeneity among findings. None of the previously published network meta-analyses provided a threshold for clinical significance and focused on statistical significance. The Cochrane review published in 2008 suggested a risk difference greater than 15% was considered clinically important (32). An examination of the analysis through this perspective yields identical answers to statistical significance in this case, as most significant odds ratios have estimates indicating at least a 15% decrease in odds compared to those taking placebo.

4.4.3 STRENGTHS AND LIMITATIONS

The results of this network meta-analysis are believed to be robust as the review was conducted according to the accepted methodology for systematic reviews. The literature search conducted by an experienced information specialist was comprehensive, covering multiple databases with a peer-reviewed search strategy. Sensitivity analyses were undertaken to determine the robustness of findings in relation to assumptions made during the network meta-analysis, such as the threshold of two SD for classifying primary versus secondary prevention studies, including studies with any risk of bias, and fractures reported as efficacy or safety events.

One advantage of this network meta-analysis is the separation of doses into different nodes, which was not done for most other NMAs found in literature. For example, the study by Liu et al. (2017) combined all doses of risedronate and alendronate. However, there may be a difference between various doses of bisphosphonates since there are separate indications for the same bisphosphonate based on dose. For example, alendronate 5 mg/day is indicated for prevention of osteoporosis while 10 mg/day is indicated for treatment. In our results, it appears that there was greater efficacy for fracture prevention observed among those taking the 10 mg dose compared to the 5 mg dose. However, we did not observe other bisphosphonates such as etidronate and risedronate showing a similar effect.

Another strength of this NMA is the large number of included studies, providing greater power to detect potentially significant differences between treatments, as well as the addition of combination treatments into the network, which was not observed in any of the NMAs found in literature. With increasing evidence for the efficacy of bisphosphonates, questions arose as to whether other anti-osteoporotic treatments can work synergistically with bisphosphonates. The studies using BMD as endpoints have found mixed results. For example, one study indicating a significant increase in spinal BMD among those treated with combination interventions compared to a single bisphosphonate (186) but another observed no difference between treatment groups (187). The current analysis did not find evidence of a significantly greater fracture prevention effect among

combinations compared to single bisphosphonate treatments. However, one significant comparison was found among safety outcomes, where alendronate 10 mg/day combined with hormone replacement therapy was associated with significantly higher odds of gastrointestinal adverse events compared to etidronate 400 mg/day. Overall, there are few included studies assessed combination treatments, thus it is also possible we are lacking power to detect any potential effects.

Limitations of this analysis include a low number of studies found that examined combination treatments, durations longer than three years, and studies examining off-label drugs for osteoporosis such as tiludronate, neridronate, and pamidronate. These diminished the power of the analysis to detect significant differences among combination treatments, long-term bisphosphonate therapy, and non-approved bisphosphonates for fracture prevention. The low number of rare adverse events observed did not allow for meaningful analysis. A follow-up review including observational studies may be more comprehensive given that randomized, controlled trials have already been covered in the current analysis. There were also few trials assessing minodronate or clodronate although they are listed as approved based on clinical practice guidelines, which may be due to these drugs being only approved in Italy and Japan. Additionally, due to the resource-intensive nature of fracture efficacy trials, there are few head-to-head trials between multiple bisphosphonates.

A methodological limitation that may have contributed to increased risk of bias is unclear study reporting. Specifically, trials that lacked specifications regarding randomization and allocation concealment methods. These studies may describe that randomization was done, however they are judged as unclear instead of low risk of bias because the method of randomization or allocation concealment was not reported. We also used a cutoff of one year treatment duration with follow-up for including trials. While the threshold aimed to set a manageable scope that allowed focus on fracture trials, the limitation is loss of data from trials with less than one year duration that may report short-term safety outcomes. It is possible that these adverse events will be captured in long-term studies that include short-term effects, however it is nonetheless a loss of potentially important data.

A source of heterogeneity is the lack of a standard method of reporting fractures. Fractures not assessed as the primary outcome were typically reported as safety adverse events. These included reporting fractures as total number of events without distinction between treatment groups, or generally as having occurred during the trial without specifying the numbers or site of fracture. It is also unclear in some studies that reported no fracture events whether a morphometric or radiographic assessment of vertebral fractures was conducted. This presents a source of heterogeneity that may be remedied in future studies by more rigorous reporting of fracture incidence.

Another potential source of heterogeneity is the lack of uniform definitions for non-vertebral fractures. In order to gather a representative evidence base for non-vertebral fracture incidence, we included fracture data that reported any type of non-vertebral fracture as defined by the study authors. While this captured all types of non-vertebral fractures found within the literature search, it also led to greater variability in the data included as “non-vertebral fracture”. Some studies may have used a definition of any fracture other than the spine, while others may have utilized a definition excluding fractures in the digits or the ankle because they could be caused by physical trauma rather than low bone mineral density (98). However, studies that do not clearly mark this distinction would be extracted and analyzed together under non-vertebral fractures. This variability may have contributed to inconsistency in the effect estimates for non-vertebral fractures. The issue has been explored in literature. A study by MacKey et al. (2011) assessed the impact of varying definitions of non-vertebral fracture on treatment effects based on data from five trials (99). They re-analyzed non-vertebral fracture efficacy according to different definitions of the outcome (*e.g.,* any non-vertebral fracture, low-trauma non-vertebral fractures only, any non-vertebral fracture excluding the face and extremities). They found the summary hazard ratios were similar regardless of fracture definitions, ranging from 0.73 to 0.78 with overlapping confidence intervals. The authors recommended the use of “any non-vertebral fracture” as the optimal definition to reduce overall sample size due to a higher likihood of events and to provide the most complete estimate of treatment benefits for patients. However, the authors pooled data from one trial each of alendronate, clodronate, zoledronic acid,

denosumab, and lasofoxifene, therefore further research is likely required with greater numbers of studies for each treatment to improve generalisability. A similar case may also occur for clinical vertebral fractures, where a fracture that is reported due to pain but confirmed radiographically would be extracted as clinical rather than morphometric because it is a symptomatic fracture. However, the trial authors may classify these fractures as radiographic or morphometric and report them as such. Thus, definitions provided by the authors regarding the type of fracture are extremely helpful for reducing misclassification.

4.4.4 CONCLUSION

Most results showed a likelihood of alendronate and zoledronic acid as the most effective therapies when compared to those taking placebo or other treatments for fracture prevention. Although evaluations of combination treatments were limited by few direct comparisons, etidronate combined with phosphate or hormone replacement therapy, and zoledronic acid combined with teriparatide showed potential of higher efficacy. The question regarding the optimal duration of long-term bisphosphonate therapy could not be clearly addressed due to few studies with longer than three years in duration. Most bisphosphonates have a similar safety profile in terms of adverse events, except for a few studies assessing off-label pamidronate and tiludronate that showed statistically significantly greater rates of withdrawal due to adverse events.

CHAPTER 5: CONCLUDING REMARKS

The methodologies of a systematic review and network meta-analysis were used to assess the efficacy and safety of bisphosphonates. Both methods allow the synthesis of pooled estimates from a foundation of clinical trials. Additionally, Bayesian network meta-analyses combine available direct evidence with indirect comparisons to condense a large quantity of information into probabilities of treatments being better than one another. For this reason, systematic reviews and network meta-analysis have been adopted into health technology assessment agencies aid decision making and guideline development.

In this analysis, we examined approved and non-approved bisphosphonates administered alone or with other interventions. Results were mostly consistent with previous findings from reviews, network meta-analyses and clinical practice guideline recommendations. The bisphosphonates etidronate, risedronate, ibandronate, and minodronate were found to be significantly better than placebo statistically for preventing vertebral fractures, while alendronate and zoledronic acid are both effective for preventing vertebral and non-vertebral fractures. Although efficacy has been observed at the level of pooled clinical trial data, generalizability of findings to the average postmenopausal osteoporosis patient varies based on individual risk factors and other issues such as adherence to treatment regimens. Non-adherence has been observed in patients taking oral bisphosphonates, mitigating potential clinical benefits of the intervention and increasing risk of fracture (188). Estimates of treatment persistence range from 10% to 78% within the first year of treatment and are lower among daily compared to weekly or monthly dosing (189). More research is required to identify not only the most effective treatments, but also how to effectively implement them in high risk populations. With increase in the population of postmenopausal women, future directions for bisphosphonate research are likely to focus on optimal combination, long-term bisphosphonate durations, as well as methods to deliver the most efficacious treatments to patients with the highest risk of fracture. In terms of reporting data, stricter rules for reporting of safety adverse events and fracture outcomes would facilitate the extraction of data in future reviews.

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APPENDIX 1: SEARCH STRATEGY FOR ALENDRONATE

Alendronate

Database: Embase Classic+Embase <1947 to 2017 August 25>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> 2017 Aug 26

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1 Osteoporosis, Postmenopausal/ (19613)
2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
7 (osteoporo* adj5 menopaus*).tw,kw. (5059)
8 (bone loss* adj5 menopaus*).tw,kw. (1577)
9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
10 (osteoporo* adj5 age-related).tw,kw. (1080)
11 (bone loss* adj5 age-related).tw,kw. (1567)
12 (osteoporo* adj5 senil*).tw,kw. (1769)
13 (bone loss* adj5 senil*).tw,kw. (50)
14 or/1-13 (42138)
15 Osteoporosis/ (147472)
16 osteoporo*.tw,kw. (179656)
17 Bone Density/ (130889)
18 (bone? adj3 densit*).tw,kw. (122854)
19 bmd.tw,kw. (69978)

20 bone loss*.tw,kw. (59493)
21 or/15-20 (342178)
22 Menopause/ (75006)
23 Postmenopause/ (85192)
24 (postmenopaus* or post-menopaus*).tw,kw. (149132)
25 or/22-24 (214833)
26 21 and 25 (54682)
27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
28 Alendronate/ (17839)
29 (aminohydroxybutane bisphosphonate or actimax or adelan or adronat or adrovance or aldren or aldrion or aldromax or aldronac or aldrox or alefos or alehelm or alenat* or alendi* or alendo or alendra* or alendris or alendro* or alenic or alenato or alend or alenvir or alenwin or aleostito or alexonal or aliot or alovell or alxis or ampine or andante or arendal or arthroplus or aurodren).tw,kw,rn. (21131)
30 (berlex or bestalen or bifemelan or bifoal seminal or bifosa* or blindafe or binosto or blocan or bonacton or bonal?n or bonapex or bonemax or bonendro* or boniran or brek or calbion or calcisedron-d or caldronate or caltera or cleveron or dargol or debenal or defixal or delfoza or deparex or difonate or discozal or doryx or drofaz or dronadil or dronal or dronatex or dronatifer or elandur or eldinir or endronax or en-por or epolar or eucalen).tw,kw,rn. (2910)
31 (filxine or findeclin or fixopan or flamisul or forosa or fortimax or fosal?n or fosamax or fosandron or fosavance or fosazom or fosfacid or fosmin or fosteo* or fostolin or fosval or genalen or gendron or glamor or holadren or jamax-s or lafedam or landrolen or ledronin or lefosan or lendral or lendronal or leodrin or lindron or lozostun or marvil or massidron or maxibone or maxtral or "minusorb mk 0217" or mk 217 or mk0217 or mk217 or morale or mosmass or nafadren or neobon or nichospor or nofrattil or nozat).tw,kw,rn. (8447)
32 (oncalst or onclast or osalen or osaston or osdr?n or osdronat or oseotenk or oseum or osficar or oslene or ossmax or osso* or ostadil or ostaham or ostalert or ostalon or ostemax or ostenan or ostenil or osteobon or osteodur or osteof* or osteomax or osteomel or osteonate or osteonorm or osteopor or osteoral or osteosan or osteotrat or osteovan or osticalcin or ostolek or ostomax).tw,kw,rn. (2311)
33 (pasodron or phostarac or porocalm or porodron or porosal or promax or ralenost or randronate or realen or regenesis or rekostin or reyoin or ridon or riledron or romax or sedron or semandrol or silidral or sinfract or siranin or strongos or synostep or teiroc or terost or tevabone or tevanate or tibolene or tilios or tivarun or tonadron or trabecan or vegabon or voroste).tw,kw,rn. (918)
34 or/28-33 [ALENDRONATE] (33858)
35 27 and 34 [ALENDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (6111)
36 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)
37 clinical trials as topic.sh. (222303)
38 exp Randomized Controlled Trials as Topic/ (260062)
39 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
40 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
41 trial.ti. (616368)
42 or/36-41 (3364349)
43 35 and 42 [RCTs - ALENDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (2440)
44 Male/ not (Female/ and Male/) (5256871)
45 43 not 44 [MALE-ONLY REMOVED] (2406)
46 exp Animals/ not (exp Animals/ and Humans/) (15473903)
47 45 not 46 [ANIMAL-ONLY REMOVED] (1950)
48 (comment or editorial or interview or news or newspaper article).pt. (1779415)
49 (letter not (letter and randomized controlled trial)).pt. (1970842)
50 47 not (48 or 49) [OPINION PIECES REMOVED] (1927)
51 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (15974685)
52 50 and 51 (273)
53 52 use ppez [MEDLINE RECORDS] (161)
54 postmenopause osteoporosis/ (13085)
55 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
56 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
57 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
58 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
59 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
60 (osteoporo* adj5 menopaus*).tw,kw. (5059)
61 (bone loss* adj5 menopaus*).tw,kw. (1577)
62 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
63 (osteoporo* adj5 age-related).tw,kw. (1080)
64 (bone loss* adj5 age-related).tw,kw. (1567)
65 (osteoporo* adj5 senil*).tw,kw. (1769)
66 (bone loss* adj5 senil*).tw,kw. (50)
67 or/54-66 (37286)
68 osteoporosis/ (147472)
69 osteoporo*.tw,kw. (179656)
70 bone density/ (130889)
71 (bone? adj3 densit*).tw,kw. (122854)
72 bmd.tw,kw. (69978)
73 bone loss*.tw,kw. (59493)
74 or/68-73 (342178)

75 menopause/ (75006)
76 postmenopause/ (85192)
77 (postmenopaus* or post-menopaus*).tw,kw. (149132)
78 or/75-77 (214833)
79 74 and 78 (54682)
80 67 or 79 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)
81 alendronic acid/ (14582)
82 (aminohydroxybutane bisphosphonate or actimax or adelan or adronat or adrovance or aldren or aldrion or aldromax or aldronac or aldrox or alefos or alehelm or alenat* or alendi* or alendo or alendra* or alendris or alendro* or alenic or alenato or alend or alenvir or alenwin or aleostito or alexonal or aliot or alovell or alxis or ampine or andante or arendal or arthroplus or aurodren).tw,kw,rn. (21131)
83 (berlex or bestalen or bifemelan or bifoal seminal or bifosa* or blindafe or binosto or blocan or bonacton or bonal?n or bonapex or bonemax or bonendro* or boniran or brek or calbion or calcisedron-d or caldronate or caltera or cleveron or dargol or debenal or defixal or delfoza or deparex or difonate or discozal or doryx or drofaz or dronadil or dronal or dronatex or dronatifer or elandur or eldinir or endronax or en-por or epolar or eucalen).tw,kw,rn. (2910)
84 (filxine or findeclin or fixopan or flamisul or forosa or fortimax or fosal?n or fosamax or fosandron or fosavance or fosazom or fosfacid or fosmin or fosteo* or fostolin or fosval or genalen or gendron or glamor or holadren or jamax-s or lafedam or landrolen or ledronin or lefosan or lendral or lendronal or leodrin or lindron or lozostun or marvil or massidron or maxibone or maxtral or "minusorb mk 0217" or mk 217 or mk0217 or mk217 or morale or mosmass or nafadren or neobon or nichospor or nofrattil or nozat).tw,kw,rn. (8447)
85 (oncalst or onclast or osalen or osaston or osdr?n or osdronat or oseotenk or oseum or osficar or oslene or ossmax or osso* or ostadil or ostaham or ostalert or ostalon or ostemax or ostenan or ostenil or osteobon or osteodur or osteof* or osteomax or osteomel or osteonate or osteonorm or osteopor or osteoral or osteosan or osteotrat or osteovan or osticalcin or ostolek or ostomax).tw,kw,rn. (2311)
86 (pasodron or phostarac or porocalm or porodron or porosal or promax or ralenost or randronate or realen or regenesis or rekostin or reyoin or ridon or riledron or romax or sedron or semandrol or silidral or sinfract or siranin or strongos or synostep or teiroc or terost or tevabone or tevanate or tibolene or tilios or tivarun or tonadron or trabecan or vegabon or voroste).tw,kw,rn. (918)
87 or/81-86 [ALENDRONATE] (33838)
88 80 and 87 [ALENDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (6247)
89 randomized controlled trial/ (945706)
90 controlled clinical study/ (447552)
91 exp "clinical trial (topic)"/ (249995)
92 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
93 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
94 trial.ti. (616368)
95 or/89-94 (3296129)
96 88 and 95 [ALENDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (2537)
97 male/ not (female/ and male/) (5256871)
98 96 not 97 [MALE-ONLY REMOVED] (2500)
99 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)
100 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)
101 99 not 100 (10086636)
102 98 not 101 [ANIMAL-ONLY REMOVED] (2462)
103 editorial.pt. (994267)
104 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)
105 102 not (103 or 104) [OPINION PIECES REMOVED] (2438)
106 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc,dd. (33782413)
107 105 and 106 (1347)
108 107 use emczd [EMBASE RECORDS] (1206)
109 Osteoporosis, Postmenopausal/ (19613)
110 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)
111 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)
112 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)
113 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)
114 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)
115 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)
116 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)
117 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)
118 (osteoporo* adj5 age-related).ti,ab,kw. (1080)
119 (bone loss* adj5 age-related).ti,ab,kw. (1567)
120 (osteoporo* adj5 senil*).ti,ab,kw. (1769)
121 (bone loss* adj5 senil*).ti,ab,kw. (50)
122 or/109-121 (42138)
123 Osteoporosis/ (147472)
124 osteoporo*.ti,ab,kw. (179656)
125 Bone Density/ (130889)
126 (bone? adj3 densit*).ti,ab,kw. (122853)
127 bmd.ti,ab,kw. (69965)
128 bone loss*.ti,ab,kw. (59493)
129 or/123-128 (342166)

130 Menopause/ (75006)
131 Postmenopause/ (85192)
132 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)
133 or/130-132 (214833)
134 129 and 133 (54682)
135 122 or 134 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
136 Alendronate/ (17839)
137 (aminohydroxybutane bisphosphonate or actimax or adelan or adronat or adrovance or aldren or aldrion or aldromax or aldronac or aldrox or alefos or alehelm or alenat* or alendi* or alendo or alendra* or alendris or alendro* or alenic or alenato or alend or alenvir or alenwin or aleostito or alexonal or aliot or alovell or alxis or ampine or andante or arendal or arthroplus or aurodren).ti,ab,kw. (11830)
138 (berlex or bestalen or bifemelan or bifoal seminal or bifosa* or blindafe or binosto or blocan or bonacton or bonal?n or bonapex or bonemax or bonendro* or boniran or brek or calbion or calcisedron-d or caldronate or caltera or cleveron or dargol or debenal or defixal or delfoza or deparex or difonate or discozal or doryx or drofaz or dronadil or dronal or dronatex or dronatifer or elandur or eldinir or endronax or en-por or epolar or eucalen).ti,ab,kw. (267)
139 (filxine or findeclin or fixopan or flamisul or forosa or fortimax or fosal?n or fosamax or fosandron or fosavance or fosazom or fosfacid or fosmin or fosteo* or fostolin or fosval or genalen or gendron or glamor or holadren or jamax-s or lafedam or landrolen or ledronin or lefosan or lendral or lendronal or leodrin or lindron or lozostun or marvil or massidron or maxibone or maxtral or "minusorb mk 0217" or mk 217 or mk0217 or mk217 or morale or mosmass or nafadren or neobon or nichospor or nofrattil or nozat).ti,ab,kw. (7030)
140 (oncalst or onclast or osalen or osaston or osdr?n or osdronat or oseotenk or oseum or osficar or oslene or ossmax or osso* or ostadil or ostaham or ostalert or ostalon or ostemax or ostenan or ostenil or osteobon or osteodur or osteof* or osteomax or osteomel or osteonate or osteonorm or osteopor or osteoral or osteosan or osteotrat or osteovan or osticalcin or ostolek or ostomax).ti,ab,kw. (2127)
141 (pasodron or phostarac or porocalm or porodron or porosal or promax or ralenost or randronate or realen or regenesis or rekostin or reyoin or ridon or riledron or romax or sedron or semandrol or silidral or sinfract or siranin or strongos or synostep or teiroc or terost or tevabone or tevanate or tibolene or tilios or tivarun or tonadron or trabecan or vegabon or voroste).ti,ab,kw. (902)
142 or/136-141 [ALENDRONATE] (30672)
143 135 and 142 [ALENDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (6019)
144 Male/ not (Female/ and Male/) (5256871)
145 143 not 144 [MALE-ONLY REMOVED] (5949)
146 ("201112" or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).up. (62320674)
147 145 and 146 (5780)
148 147 use cctr [CENTRAL RECORDS] (554)
149 53 or 108 or 148 [ALL DATABASES] (1921)
150 remove duplicates from 149 (1397) [TOTAL UNIQUE RECORDS]
151 150 use ppez [MEDLINE UNIQUE RECORDS] (142)
152 150 use emczd [EMBASE UNIQUE RECORDS] (1087)
153 150 use cctr [CENTRAL UNIQUE RECORDS] (168)

APPENDIX 2: SEARCH STRATEGIES FOR OTHER BISPHOSPHONATES

Alendronate (see Appendix 1)

Etidronate

Database: Embase Classic+Embase <1947 to 2017 August 25>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> 2017 Aug 26

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1 Osteoporosis, Postmenopausal/ (19613)
2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
7 (osteoporo* adj5 menopaus*).tw,kw. (5059)
8 (bone loss* adj5 menopaus*).tw,kw. (1577)
9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
10 (osteoporo* adj5 age-related).tw,kw. (1080)
11 (bone loss* adj5 age-related).tw,kw. (1567)
12 (osteoporo* adj5 senil*).tw,kw. (1769)
13 (bone loss* adj5 senil*).tw,kw. (50)
14 or/1-13 (42138)
15 Osteoporosis/ (147472)
16 osteoporo*.tw,kw. (179656)
17 Bone Density/ (130889)
18 (bone? adj3 densit*).tw,kw. (122854)

19 bmd.tw,kw. (69978)
20 bone loss*.tw,kw. (59493)
21 or/15-20 (342178)
22 Menopause/ (75006)
23 Postmenopause/ (85192)
24 (postmenopaus* or post-menopaus*).tw,kw. (149132)
25 or/22-24 (214833)
26 21 and 25 (54682)
27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
28 Etidronic Acid/ (9990)
29 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (29824)
30 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (76319)
31 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (207)
32 or/28-31 [ETIDRONATE] (102208)
33 27 and 32 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3920)
34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)
35 clinical trials as topic.sh. (222303)
36 exp Randomized Controlled Trials as Topic/ (260062)
37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
39 trial.ti. (616368)
40 or/34-39 (3364349)
41 33 and 40 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1425)
42 Male/ not (Female/ and Male/) (5256871)
43 41 not 42 [MALE-ONLY REMOVED] (1403)
44 exp Animals/ not (exp Animals/ and Humans/) (15473903)
45 43 not 44 [ANIMAL-ONLY REMOVED] (1342)
46 (comment or editorial or interview or news or newspaper article).pt. (1779415)
47 (letter not (letter and randomized controlled trial)).pt. (1970842)
48 45 not (46 or 47) [OPINION PIECES REMOVED] (1319)
49 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (15974685)
50 48 and 49 (197)
51 50 use ppez [MEDLINE RECORDS] (189)
52 postmenopause osteoporosis/ (13085)
53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
56 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
57 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
58 (osteoporo* adj5 menopaus*).tw,kw. (5059)
59 (bone loss* adj5 menopaus*).tw,kw. (1577)
60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
61 (osteoporo* adj5 age-related).tw,kw. (1080)
62 (bone loss* adj5 age-related).tw,kw. (1567)
63 (osteoporo* adj5 senil*).tw,kw. (1769)
64 (bone loss* adj5 senil*).tw,kw. (50)
65 or/52-64 (37286)
66 osteoporosis/ (147472)
67 osteoporo*.tw,kw. (179656)
68 bone density/ (130889)
69 (bone? adj3 densit*).tw,kw. (122854)
70 bmd.tw,kw. (69978)
71 bone loss*.tw,kw. (59493)
72 or/66-71 (342178)
73 menopause/ (75006)
74 postmenopause/ (85192)
75 (postmenopaus* or post-menopaus*).tw,kw. (149132)
76 or/73-75 (214833)
77 72 and 76 (54682)
78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)
79 etidronic acid/ (9990)
80 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (29824)

81 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (76319)
82 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (207)
83 or/79-82 [ETIDRONATE] (102208)
84 78 and 83 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3384)
85 randomized controlled trial/ (945706)
86 controlled clinical study/ (447552)
87 exp "clinical trial (topic)"/ (249995)
88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
90 trial.ti. (616368)
91 or/85-90 (3296129)
92 84 and 91 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1204)
93 male/ not (female/ and male/) (5256871)
94 92 not 93 [MALE-ONLY REMOVED] (1188)
95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)
96 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)
97 95 not 96 (10086636)
98 94 not 97 [ANIMAL-ONLY REMOVED] (1179)
99 editorial.pt. (994267)
100 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)
101 98 not (99 or 100) [OPINION PIECES REMOVED] (1174)
102 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc,dd. (33782413)
103 101 and 102 (475)
104 103 use emczd [EMBASE RECORDS] (323)
105 Osteoporosis, Postmenopausal/ (19613)
106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)
107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)
108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)
109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)
110 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)
111 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)
112 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)
113 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)
114 (osteoporo* adj5 age-related).ti,ab,kw. (1080)
115 (bone loss* adj5 age-related).ti,ab,kw. (1567)
116 (osteoporo* adj5 senil*).ti,ab,kw. (1769)
117 (bone loss* adj5 senil*).ti,ab,kw. (50)
118 or/105-117 (42138)
119 Osteoporosis/ (147472)
120 osteoporo*.ti,ab,kw. (179656)
121 Bone Density/ (130889)
122 (bone? adj3 densit*).ti,ab,kw. (122853)
123 bmd.ti,ab,kw. (69965)
124 bone loss*.ti,ab,kw. (59493)
125 or/119-124 (342166)
126 Menopause/ (75006)
127 Postmenopause/ (85192)
128 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)
129 or/126-128 (214833)
130 125 and 129 (54682)
131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
132 Etidronic Acid/ (9990)
133 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).ti,ab,kw. (10114)
134 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).ti,ab,kw. (67847)
135 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).ti,ab,kw. (57)
136 or/132-135 [ETIDRONATE] (83297)
137 131 and 136 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (2293)
138 Male/ not (Female/ and Male/) (5256871)
139 137 not 138 [MALE-ONLY REMOVED] (2264)
140 ("201112" or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).up. (62320674)
141 139 and 140 (2254)
142 141 use cctr [CENTRAL RECORDS] (217)
143 51 or 104 or 142 [ALL DATABASES] (729)
144 remove duplicates from 143 (606) [TOTAL UNIQUE RECORDS]
145 144 use ppez [MEDLINE UNIQUE RECORDS] (169)

146 144 use emczd [EMBASE UNIQUE RECORDS] (305)
147 144 use cctr [CENTRAL UNIQUE RECORDS] (132)

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Risedronate

Database: Embase Classic+Embase <1947 to 2017 August 25>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

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1 Osteoporosis, Postmenopausal/ (19613)
2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
7 (osteoporo* adj5 menopaus*).tw,kw. (5059)
8 (bone loss* adj5 menopaus*).tw,kw. (1577)
9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
10 (osteoporo* adj5 age-related).tw,kw. (1080)
11 (bone loss* adj5 age-related).tw,kw. (1567)
12 (osteoporo* adj5 senil*).tw,kw. (1769)
13 (bone loss* adj5 senil*).tw,kw. (50)
14 or/1-13 (42138)
15 Osteoporosis/ (147472)
16 osteoporo*.tw,kw. (179656)
17 Bone Density/ (130889)
18 (bone? adj3 densit*).tw,kw. (122854)
19 bmd.tw,kw. (69978)
20 bone loss*.tw,kw. (59493)
21 or/15-20 (342178)
22 Menopause/ (75006)
23 Postmenopause/ (85192)
24 (postmenopaus* or post-menopaus*).tw,kw. (149132)
25 or/22-24 (214833)
26 21 and 25 (54682)
27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
28 Risedronate Sodium/ (8483)
29 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).tw,kw,rn. (20923)
30 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).tw,kw,rn. (67)
31 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).tw,kw,rn. (4186)
32 or/28-31 [RISEDRONATE] (25089)
33 27 and 32 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3131)
34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)
35 clinical trials as topic.sh. (222303)
36 exp Randomized Controlled Trials as Topic/ (260062)
37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
39 trial.ti. (616368)
40 or/34-39 (3364349)
41 33 and 40 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1177)
42 Male/ not (Female/ and Male/) (5256871)
43 41 not 42 [MALE-ONLY REMOVED] (1161)
44 exp Animals/ not (exp Animals/ and Humans/) (15473903)
45 43 not 44 [ANIMAL-ONLY REMOVED] (931)
46 (comment or editorial or interview or news or newspaper article).pt. (1779415)
47 (letter not (letter and randomized controlled trial)).pt. (1970842)
48 45 not (46 or 47) [OPINION PIECES REMOVED] (920)
49 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (15974685)
50 48 and 49 (128)
51 50 use ppez [MEDLINE RECORDS] (83)
52 postmenopause osteoporosis/ (13085)
53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
56 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
57 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
58 (osteoporo* adj5 menopaus*).tw,kw. (5059)

59 (bone loss* adj5 menopaus*).tw,kw. (1577)
60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
61 (osteoporo* adj5 age-related).tw,kw. (1080)
62 (bone loss* adj5 age-related).tw,kw. (1567)
63 (osteoporo* adj5 senil*).tw,kw. (1769)
64 (bone loss* adj5 senil*).tw,kw. (50)
65 or/52-64 (37286)
66 osteoporosis/ (147472)
67 osteoporo*.tw,kw. (179656)
68 bone density/ (130889)
69 (bone? adj3 densit*).tw,kw. (122854)
70 bmd.tw,kw. (69978)
71 bone loss*.tw,kw. (59493)
72 or/66-71 (342178)
73 menopause/ (75006)
74 postmenopause/ (85192)
75 (postmenopaus* or post-menopaus*).tw,kw. (149132)
76 or/73-75 (214833)
77 72 and 76 (54682)
78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)
79 risedronic acid/ (8252)
80 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).tw,kw,rn. (20923)
81 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).tw,kw,rn. (67)
82 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).tw,kw,rn. (4186)
83 or/79-82 [RISEDRONATE] (25085)
84 78 and 83 [RISEDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3349)
85 randomized controlled trial/ (945706)
86 controlled clinical study/ (447552)
87 exp "clinical trial (topic)"/ (249995)
88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
90 trial.ti. (616368)
91 or/85-90 (3296129)
92 84 and 91 [RISEDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1229)
93 male/ not (female/ and male/) (5256871)
94 92 not 93 [MALE-ONLY REMOVED] (1213)
95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)
96 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)
97 95 not 96 (10086636)
98 94 not 97 [ANIMAL-ONLY REMOVED] (1204)
99 editorial.pt. (994267)
100 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)
101 98 not (99 or 100) [OPINION PIECES REMOVED] (1193)
102 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc,dd. (33782413)
103 101 and 102 (698)
104 103 use emczd [EMBASE RECORDS] (631)
105 Osteoporosis, Postmenopausal/ (19613)
106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)
107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)
108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)
109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)
110 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)
111 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)
112 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)
113 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)
114 (osteoporo* adj5 age-related).ti,ab,kw. (1080)
115 (bone loss* adj5 age-related).ti,ab,kw. (1567)
116 (osteoporo* adj5 senil*).ti,ab,kw. (1769)
117 (bone loss* adj5 senil*).ti,ab,kw. (50)
118 or/105-117 (42138)
119 Osteoporosis/ (147472)
120 osteoporo*.ti,ab,kw. (179656)
121 Bone Density/ (130889)
122 (bone? adj3 densit*).ti,ab,kw. (122853)
123 bmd.ti,ab,kw. (69965)
124 bone loss*.ti,ab,kw. (59493)
125 or/119-124 (342166)
126 Menopause/ (75006)

127 Postmenopause/ (85192)
128 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)
129 or/126-128 (214833)
130 125 and 129 (54682)
131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
132 Risedronate Sodium/ (8483)
133 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).ti,ab,kw. (6600)
134 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).ti,ab,kw. (33)
135 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).ti,ab,kw. (1692)
136 or/132-135 [RISEDRONATE] (13223)
137 131 and 136 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3121)
138 Male/ not (Female/ and Male/) (5256871)
139 137 not 138 [MALE-ONLY REMOVED] (3089)
140 ("201112" or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).up. (62320674)
141 139 and 140 (3006)
142 141 use cctr [CENTRAL RECORDS] (206)
143 51 or 104 or 142 [ALL DATABASES] (920)
144 remove duplicates from 143 (702)
145 144 use ppez [MEDLINE UNIQUE RECORDS] (69)
146 144 use emczd [EMBASE UNIQUE RECORDS] (573)
147 144 use cctr [CENTRAL UNIQUE RECORDS] (60)
****

Zoledronic Acid

Database: Embase Classic+Embase <1947 to 2017 August 25>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

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1 Osteoporosis, Postmenopausal/ (19613)
2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
7 (osteoporo* adj5 menopaus*).tw,kw. (5059)
8 (bone loss* adj5 menopaus*).tw,kw. (1577)
9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
10 (osteoporo* adj5 age-related).tw,kw. (1080)
11 (bone loss* adj5 age-related).tw,kw. (1567)
12 (osteoporo* adj5 senil*).tw,kw. (1769)
13 (bone loss* adj5 senil*).tw,kw. (50)
14 or/1-13 (42138)
15 Osteoporosis/ (147472)
16 osteoporo*.tw,kw. (179656)
17 Bone Density/ (130889)
18 (bone? adj3 densit*).tw,kw. (122854)
19 bmd.tw,kw. (69978)
20 bone loss*.tw,kw. (59493)
21 or/15-20 (342178)
22 Menopause/ (75006)
23 Postmenopause/ (85192)
24 (postmenopaus* or post-menopaus*).tw,kw. (149132)
25 or/22-24 (214833)
26 21 and 25 (54682)
27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
28 (zolendronate or zoledronic acid or aclasta).tw,kw,rn. (18607)
29 (cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or db00399).tw,kw,rn. (32)
30 (orazol or reclast or zol 446 or zol446 or zolendron* or zometa or zomera).tw,kw,rn. (2052)
31 or/28-30 [ZOLEDRONIC ACID] (18821)
32 27 and 31 [ZOLEDRONIC ACID IN POSTMENOPAUSAL OSTEOPOROSIS] (2187)
33 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)
34 clinical trials as topic.sh. (222303)
35 exp Randomized Controlled Trials as Topic/ (260062)
36 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
37 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
38 trial.ti. (616368)
39 or/33-38 (3364349)
40 32 and 39 [ZOLEDRONIC ACID IN POSTMENOPAUSAL OSTEOPOROSIS] (835)

41 Male/ not (Female/ and Male/) (5256871)
42 40 not 41 [MALE-ONLY REMOVED] (816)
43 exp Animals/ not (exp Animals/ and Humans/) (15473903)
44 42 not 43 [ANIMAL-ONLY REMOVED] (553)
45 (comment or editorial or interview or news or newspaper article).pt. (1779415)
46 (letter not (letter and randomized controlled trial)).pt. (1970842)
47 44 not (45 or 46) [OPINION PIECES REMOVED] (550)
48 (201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (17346906)
49 47 and 48 (204)
50 49 use ppez [MEDLINE RECORDS] (104)
51 postmenopause osteoporosis/ (13085)
52 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
53 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
54 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
55 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
56 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
57 (osteoporo* adj5 menopaus*).tw,kw. (5059)
58 (bone loss* adj5 menopaus*).tw,kw. (1577)
59 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
60 (osteoporo* adj5 age-related).tw,kw. (1080)
61 (bone loss* adj5 age-related).tw,kw. (1567)
62 (osteoporo* adj5 senil*).tw,kw. (1769)
63 (bone loss* adj5 senil*).tw,kw. (50)
64 or/51-63 (37286)
65 osteoporosis/ (147472)
66 osteoporo*.tw,kw. (179656)
67 bone density/ (130889)
68 (bone? adj3 densit*).tw,kw. (122854)
69 bmd.tw,kw. (69978)
70 bone loss*.tw,kw. (59493)
71 or/65-70 (342178)
72 menopause/ (75006)
73 postmenopause/ (85192)
74 (postmenopaus* or post-menopaus*).tw,kw. (149132)
75 or/72-74 (214833)
76 71 and 75 (54682)
77 64 or 76 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)
78 zoledronic acid/ (13700)
79 (zolendronate or zoledronic acid or aclasta).tw,kw,rn. (18607)
80 (cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or db00399).tw,kw,rn. (32)
81 (orazol or reclast or zol 446 or zol446 or zolendron* or zometa or zomera).tw,kw,rn. (2052)
82 or/78-81 [ZOLEDRONIC ACID] (19189)
83 77 and 82 [ZOLEDRONIC ACID - POST-MENOPAUSAL OSTEOPOROSIS] (2502)
84 randomized controlled trial/ (945706)
85 controlled clinical study/ (447552)
86 exp "clinical trial (topic)"/ (249995)
87 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
88 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
89 trial.ti. (616368)
90 or/84-89 (3296129)
91 83 and 90 [ZOLEDRONIC ACID - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (971)
92 male/ not (female/ and male/) (5256871)
93 91 not 92 [MALE-ONLY REMOVED] (949)
94 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)
95 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)
96 94 not 95 (10086636)
97 93 not 96 [ANIMAL-ONLY REMOVED] (934)
98 editorial.pt. (994267)
99 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)
100 97 not (98 or 99) [OPINION PIECES REMOVED] (925)
101 (201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc,dd. (34802102)
102 100 and 101 (656)
103 102 use emczd [EMBASE RECORDS] (568)
104 Osteoporosis, Postmenopausal/ (19613)
105 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)
106 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)
107 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)
108 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)

109 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)
110 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)
111 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)
112 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)
113 (osteoporo* adj5 age-related).ti,ab,kw. (1080)
114 (bone loss* adj5 age-related).ti,ab,kw. (1567)
115 (osteoporo* adj5 senil*).ti,ab,kw. (1769)
116 (bone loss* adj5 senil*).ti,ab,kw. (50)
117 or/104-115 (42131)
118 Osteoporosis/ (147472)
119 osteoporo*.ti,ab,kw. (179656)
120 Bone Density/ (130889)
121 (bone? adj3 densit*).ti,ab,kw. (122853)
122 bmd.ti,ab,kw. (69965)
123 bone loss*.ti,ab,kw. (59493)
124 or/118-123 (342166)
125 Menopause/ (75006)
126 Postmenopause/ (85192)
127 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)
128 or/125-127 (214833)
129 124 and 128 (54682)
130 117 or 129 [POST-MENOPAUSAL OSTEOPOROSIS] (66415)
131 (zolendronate or zoledronic acid or aclasta).ti,ab,kw. (9481)
132 (cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or db00399).ti,ab,kw. (19)
133 (orazol or reclast or zol 446 or zol446 or zolendron* or zometa or zomera).ti,ab,kw. (817)
134 or/131-133 [ZOLEDRONIC ACID] (9802)
135 130 and 134 [ZOLEDRONIC ACID IN POSTMENOPAUSAL OSTEOPOROSIS] (1208)
136 Male/ not (Female/ and Male/) (5256871)
137 135 not 136 [MALE-ONLY REMOVED] (1183)
138 ("201105" or "201106" or "201107" or "201108" or "201109" or "201110" or "201111" or "201112" or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).up. (62320674)
139 137 and 138 (1091)
140 139 use cctr [CENTRAL RECORDS] (143)
141 50 or 103 or 140 [ALL DATABASES] (815)
142 remove duplicates from 141 (639) [TOTAL UNIQUE RECORDS]
143 142 use ppez [MEDLINE UNIQUE RECORDS] (96)
144 142 use emczd [EMBASE RECORDS] (491)
145 142 use cctr [CENTRAL RECORDS] (52)

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Ibandronate

Database: Embase Classic+Embase <1947 to 2017 August 25>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 Osteoporosis, Postmenopausal/ (19613)
2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
7 (osteoporo* adj5 menopaus*).tw,kw. (5059)
8 (bone loss* adj5 menopaus*).tw,kw. (1577)
9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
10 (osteoporo* adj5 age-related).tw,kw. (1080)
11 (bone loss* adj5 age-related).tw,kw. (1567)
12 (osteoporo* adj5 senil*).tw,kw. (1769)
13 (bone loss* adj5 senil*).tw,kw. (50)
14 or/1-13 (42138)
15 Osteoporosis/ (147472)
16 osteoporo*.tw,kw. (179656)
17 Bone Density/ (130889)
18 (bone? adj3 densit*).tw,kw. (122854)
19 bmd.tw,kw. (69978)
20 bone loss*.tw,kw. (59493)
21 or/15-20 (342178)
22 Menopause/ (75006)
23 Postmenopause/ (85192)

24 (postmenopaus* or post-menopaus*).tw,kw. (149132)
25 or/22-24 (214833)
26 21 and 25 (54682)
27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
28 (ibandron* or bm 210955 or bm210955 or bonat or bondenza or bondronat* or boniva or bonviva or destara or iasibon or r 484 or r484).tw,kw,rn. [IBANDRONATE] (6388)
29 27 and 28 [IBANDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1803)
30 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)
31 clinical trials as topic.sh. (222303)
32 exp Randomized Controlled Trials as Topic/ (260062)
33 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
34 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
35 trial.ti. (616368)
36 or/30-35 (3364349)
37 29 and 36 [IBANDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (691)
38 Male/ not (Female/ and Male/) (5256871)
39 37 not 38 [MALE-ONLY REMOVED] (680)
40 exp Animals/ not (exp Animals/ and Humans/) (15473903)
41 39 not 40 [ANIMAL-ONLY REMOVED] (485)
42 (comment or editorial or interview or news or newspaper article).pt. (1779415)
43 (letter not (letter and randomized controlled trial)).pt. (1970842)
44 41 not (42 or 43) [OPINION PIECES REMOVED] (483)
45 (201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (17346906)
46 44 and 45 (113)
47 46 use ppez [MEDLINE RECORDS] (55)
48 postmenopause osteoporosis/ (13085)
49 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
50 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
51 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
52 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
53 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
54 (osteoporo* adj5 menopaus*).tw,kw. (5059)
55 (bone loss* adj5 menopaus*).tw,kw. (1577)
56 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
57 (osteoporo* adj5 age-related).tw,kw. (1080)
58 (bone loss* adj5 age-related).tw,kw. (1567)
59 (osteoporo* adj5 senil*).tw,kw. (1769)
60 (bone loss* adj5 senil*).tw,kw. (50)
61 or/48-60 (37286)
62 osteoporosis/ (147472)
63 osteoporo*.tw,kw. (179656)
64 bone density/ (130889)
65 (bone? adj3 densit*).tw,kw. (122854)
66 bmd.tw,kw. (69978)
67 bone loss*.tw,kw. (59493)
68 or/62-67 (342178)
69 menopause/ (75006)
70 postmenopause/ (85192)
71 (postmenopaus* or post-menopaus*).tw,kw. (149132)
72 or/69-71 (214833)
73 68 and 72 (54682)
74 61 or 73 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)
75 ibandronic acid/ (4823)
76 (ibandron* or bm 210955 or bm210955 or bonat or bondenza or bondronat* or boniva or bonviva or destara or iasibon or r 484 or r484).tw,kw,rn. (6388)
77 or/75-76 [IBANDRONATE] (6388)
78 74 and 77 [IBANDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (2010)
79 randomized controlled trial/ (945706)
80 controlled clinical study/ (447552)
81 exp "clinical trial (topic)"/ (249995)
82 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
83 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
84 trial.ti. (616368)
85 or/79-84 (3296129)
86 78 and 85 [IBANDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (769)
87 male/ not (female/ and male/) (5256871)
88 86 not 87 [MALE-ONLY REMOVED] (755)
89 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)
90 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)

91 89 not 90 (10086636)
92 88 not 91 [ANIMAL-ONLY REMOVED] (750)
93 editorial.pt. (994267)
94 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)
95 92 not (93 or 94) [OPINION PIECES REMOVED] (743)
96 (201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc,dd. (34802102)
97 95 and 96 (500)
98 97 use emczd [EMBASE RECORDS] (450)
99 Osteoporosis, Postmenopausal/ (19613)
100 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)
101 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)
102 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)
103 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)
104 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)
105 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)
106 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)
107 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)
108 (osteoporo* adj5 age-related).ti,ab,kw. (1080)
109 (bone loss* adj5 age-related).ti,ab,kw. (1567)
110 (osteoporo* adj5 senil*).ti,ab,kw. (1769)
111 (bone loss* adj5 senil*).ti,ab,kw. (50)
112 or/99-111 (42138)
113 Osteoporosis/ (147472)
114 osteoporo*.ti,ab,kw. (179656)
115 Bone Density/ (130889)
116 (bone? adj3 densit*).ti,ab,kw. (122853)
117 bmd.ti,ab,kw. (69965)
118 bone loss*.ti,ab,kw. (59493)
119 or/113-118 (342166)
120 Menopause/ (75006)
121 Postmenopause/ (85192)
122 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)
123 or/120-122 (214833)
124 119 and 123 (54682)
125 112 or 124 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)
126 (ibandron* or bm 210955 or bm210955 or bonat or bondenza or bondronat* or boniva or bonviva or destara or iasibon or r484 or r484).ti,ab,kw. [IBANDRONATE] (3166)
127 125 and 126 [IBANDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1044)
128 Male/ not (Female/ and Male/) (5256871)
129 127 not 128 [MALE-ONLY REMOVED] (1019)
130 ("201105" or "201106" or "201107" or "201108" or "201109" or "201110" or "201111" or "201112" or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).up. (62320674)
131 129 and 130 (959)
132 131 use cctr [CENTRAL RECORDS] (119)
133 47 or 98 or 132 [ALL DATABASES] (624)
134 remove duplicates from 133 (480) [TOTAL UNIQUE RECORDS]
135 134 use ppez [MEDLINE UNIQUE RECORDS] (52)
136 134 use emczd [EMBASE UNIQUE RECORDS] (402)
137 134 use cctr [CENTRAL RECORDS] (26)

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Clodronate, Tiludronate. Pamidronate, Neridronate, Olpadronate, Minodronate
Database: Embase Classic+Embase <1947 to 2017 August 25>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2017>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 Osteoporosis, Postmenopausal/ (19613)
2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
7 (osteoporo* adj5 menopaus*).tw,kw. (5059)
8 (bone loss* adj5 menopaus*).tw,kw. (1577)
9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
10 (osteoporo* adj5 age-related).tw,kw. (1080)
11 (bone loss* adj5 age-related).tw,kw. (1567)
12 (osteoporo* adj5 senil*).tw,kw. (1769)

13 (bone loss* adj5 senil*).tw,kw. (50)
14 or/1-12 (42131)
15 Osteoporosis/ (147472)
16 osteoporo*.tw,kw. (179656)
17 Bone Density/ (130889)
18 (bone? adj3 densit*).tw,kw. (122854)
19 bmd.tw,kw. (69978)
20 bone loss*.tw,kw. (59493)
21 or/15-20 (342178)
22 Menopause/ (75006)
23 Postmenopause/ (85192)
24 (postmenopaus* or post-menopaus*).tw,kw. (149132)
25 or/22-24 (214833)
26 21 and 25 (54682)
27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66415)
28 Diphosphonates/ (43322)
29 (diphosphonate* or bisphosphonate* or biphosphonate*).tw,kw,rn. (54357)
30 Clodronic Acid/ (7771)
31 (clodronate or abioklad or "bm 06011" or bm 6011 or bm06011 or bm6011 or bonefos or clasteon or clastoban or clodronic acid or difosfonal or lodronat or lodronate or loron or lytos or mebonat or ossiten or ostac).tw,kw,rn. (8971)
32 (Cl2MDP or dichloromethane diphosphonate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylene biphosphonate or dichloromethylene diphosphonate or dichloromethylenebisphosphonate or KCO-692).tw,kw,rn. (949)
33 (tiludronate or ClPsMBP or Cl2sMBP or Me 3737 or SR-41319 or SR-41319b or tiludronic acid or skelid).tw,kw,rn. (1028)
34 (pamidronate or aminohydroxypropylidene bisphosphonate or aminomux or APD or aredia or aredronet or cgp 23339 or cgp 23339a or cgp23339 or cgp23339a or ostepam or pamidrin or pamidro cell or pamidrocell or pamidromyl or pamidronat or pamifos or pamimed or paminject or pamimed or pamipro or pamired or pamisol or pamitor or panolin or panorin or pamidronic acid or pamimed or ribodronat or texpami).tw,kw,rn. (23955)
35 (neridronate or 6-AHHDP or AHHexBP or aminohexane bisphosphonate or neridronic acid or nerixia).tw,kw,rn. (563)
36 (olpadronate or AHGA diphosphonate or dimethyl pamidronate or ig 8801 or ig8801 or Me2-APD or olpadronic acid).tw,kw,rn. (355)
37 (minodronate or minodronic acid or bonoteo or ONO 5920 or ONO5920 or onobis or recalbon or YH 529 or YH529 or YM 529 or YM529).tw,kw,rn. (521)
38 or/28-37 [Bisphosphonates of Interest] (85188)
39 27 and 38 (9091)
40 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)
41 clinical trials as topic.sh. (222303)
42 exp Randomized Controlled Trials as Topic/ (260062)
43 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
44 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
45 trial.ti. (616368)
46 or/40-45 (3364349)
47 39 and 46 [Bisphosphonates of Interest - RCTs] (2863)
48 Male/ not (Female/ and Male/) (5256871)
49 47 not 48 [MALE-ONLY REMOVED] (2829)
50 exp Animals/ not (exp Animals/ and Humans/) (15473903)
51 49 not 50 [ANIMAL-ONLY REMOVED] (2319)
52 (comment or editorial or interview or news or newspaper article).pt. (1779415)
53 (letter not (letter and randomized controlled trial)).pt. (1970842)
54 51 not (52 or 53) [OPINION PIECES REMOVED] (2296)
55 54 use ppez [MEDLINE RECORDS] (1011)
56 postmenopause osteoporosis/ (13085)
57 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)
58 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)
59 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)
60 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)
61 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)
62 (osteoporo* adj5 menopaus*).tw,kw. (5059)
63 (bone loss* adj5 menopaus*).tw,kw. (1577)
64 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)
65 (osteoporo* adj5 age-related).tw,kw. (1080)
66 (bone loss* adj5 age-related).tw,kw. (1567)
67 (osteoporo* adj5 senil*).tw,kw. (1769)
68 (bone loss* adj5 senil*).tw,kw. (50)
69 or/56-68 (37286)
70 osteoporosis/ (147472)
71 osteoporo*.tw,kw. (179656)
72 bone density/ (130889)
73 (bone? adj3 densit*).tw,kw. (122854)
74 bmd.tw,kw. (69978)

75 bone loss*.tw,kw. (59493)
76 or/70-75 (342178)
77 menopause/ (75006)
78 postmenopause/ (85192)
79 (postmenopaus* or post-menopaus*).tw,kw. (149132)
80 or/77-79 (214833)
81 76 and 80 (54682)
82 69 or 81 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)
83 bisphosphonic acid derivative/ (30547)
84 (diphosphonate* or bisphosphonate* or biphosphonate*).tw,kw,rn. (54357)
85 clodronic acid/ (7771)
86 (clodronate or abioklad or "bm 06011" or bm 6011 or bm06011 or bm6011 or bonefos or clasteon or clastoban or clodronic acid or difosfonal or lodronat or lodronate or loron or lytos or mebonat or ossiten or ostac).tw,kw,rn. (8971)
87 (Cl2MDP or dichloromethane diphosphonate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylene biphosphonate or dichloromethylene diphosphonate or dichloromethylenebisphosphonate or KCO-692).tw,kw,rn. (949)
88 tiludronic acid/ (827)
89 (tiludronate or ClPsMBP or Cl2sMBP or Me 3737 or SR-41319 or SR-41319b or tiludronic acid or skelid).tw,kw,rn. (1028)
90 pamidronic acid/ (9702)
91 (pamidronate or aminohydroxypropylidene bisphosphonate or aminomux or APD or aredia or aredronet or cgp 23339 or cgp 23339a or cgp23339 or cgp23339a or ostepam or pamidrin or pamidro cell or pamidrocell or pamidromyl or pamidronat or pamifos or pamimed or paminject or pamimed or pamipro or pamired or pamisol or pamitor or panolin or panorin or pamidronic acid or pamimed or ribodronat or texpami).tw,kw,rn. (23955)
92 neridronic acid/ (394)
93 (neridronate or 6-AHHDP or AHHexBP or aminohexane bisphosphonate or neridronic acid or nerixia).tw,kw,rn. (563)
94 olpadronic acid/ (258)
95 (olpadronate or AHGA diphosphonate or dimethyl pamidronate or ig 8801 or ig8801 or Me2-APD or olpadronic acid).tw,kw,rn. (355)
96 minodronic acid/ (324)
97 (minodronate or minodronic acid or bonoteo or ONO 5920 or ONO5920 or onobis or recalbon or YH 529 or YH529 or YM 529 or YM529).tw,kw,rn. (521)
98 or/83-97 [Bisphosphonates of Interest] (85950)
99 82 and 98 (9174)
100 randomized controlled trial/ (945706)
101 controlled clinical study/ (447552)
102 exp "clinical trial (topic)"/ (249995)
103 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)
104 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)
105 trial.ti. (616368)
106 or/100-105 (3296129)
107 99 and 106 [Bisphosphonates of Interest - RCTs] (2845)
108 male/ not (female/ and male/) (5256871)
109 107 not 108 [MALE-ONLY REMOVED] (2814)
110 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)
111 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)
112 110 not 111 (10086636)
113 109 not 112 [ANIMAL-ONLY REMOVED] (2787)
114 editorial.pt. (994267)
115 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)
116 113 not (114 or 115) [OPINION PIECES REMOVED] (2755)
117 116 use emczd [EMBASE RECORDS] (1649)
118 Osteoporosis, Postmenopausal/ (19613)
119 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)
120 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)
121 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)
122 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)
123 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)
124 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)
125 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)
126 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)
127 (osteoporo* adj5 age-related).ti,ab,kw. (1080)
128 (bone loss* adj5 age-related).ti,ab,kw. (1567)
129 (osteoporo* adj5 senil*).ti,ab,kw. (1769)
130 (bone loss* adj5 senil*).ti,ab,kw. (50)
131 or/118-129 (42131)
132 Osteoporosis/ (147472)
133 osteoporo*.ti,ab,kw. (179656)
134 Bone Density/ (130889)
135 (bone? adj3 densit*).ti,ab,kw. (122853)
136 bmd.ti,ab,kw. (69965)

137 bone loss*.ti,ab,kw. (59493)
138 or/132-137 (342166)
139 Menopause/ (75006)
140 Postmenopause/ (85192)
141 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)
142 or/139-141 (214833)
143 138 and 142 (54682)
144 131 or 143 [POST-MENOPAUSAL OSTEOPOROSIS] (66415)
145 Diphosphonates/ (43322)
146 (diphosphonate* or bisphosphonate* or biphosphonate*).ti,ab,kw. (48743)
147 Clodronic Acid/ (7771)
148 (clodronate or abioklad or "bm 06011" or bm 6011 or bm06011 or bm6011 or bonefos or clasteon or clastoban or clodronic acid or difosfonal or lodronat or lodronate or loron or lytos or mebonat or ossiten or ostac).ti,ab,kw. (4794)
149 (Cl2MDP or dichloromethane diphosphonate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylene biphosphonate or dichloromethylene diphosphonate or dichloromethylenebisphosphonate or KCO-692).ti,ab,kw. (948)
150 (tiludronate or ClPsMBP or Cl2sMBP or Me 3737 or SR-41319 or SR-41319b or tiludronic acid or skelid).ti,ab,kw. (371)
151 (pamidronate or aminohydroxypropylidene bisphosphonate or aminomux or APD or aredia or aredronet or cgp 23339 or cgp 23339a or cgp23339 or cgp23339a or ostepam or pamidrin or pamidro cell or pamidrocell or pamidromyl or pamidronat or pamifos or pamimed or paminject or pamimed or pamipro or pamired or pamisol or pamitor or panolin or panorin or pamidronic acid or pamimed or ribodronat or texpami).ti,ab,kw. (16996)
152 (neridronate or 6-AHHDP or AHHexBP or aminohexane bisphosphonate or neridronic acid or nerixia).ti,ab,kw. (306)
153 (olpadronate or AHGA diphosphonate or dimethyl pamidronate or ig 8801 or ig8801 or Me2-APD or olpadronic acid).ti,ab,kw. (143)
154 (minodronate or minodronic acid or bonoteo or ONO 5920 or ONO5920 or onobis or recalbon or YH 529 or YH529 or YM 529 or YM529).ti,ab,kw. (361)
155 or/145-154 [Bisphosphonates of Interest] (82818)
156 144 and 155 (9033)
157 Male/ not (Female/ and Male/) (5256871)
158 156 not 157 [MALE-ONLY REMOVED] (8911)
159 158 use cctr [CENTRAL RECORDS] (576)
160 55 or 117 or 159 [ALL DATABASES] (3236)
161 remove duplicates from 160 (2032) [TOTAL UNIQUE RECORDS]
162 161 use ppez [MEDLINE UNIQUE RECORDS] (948)
163 161 use emczd [EMBASE UNIQUE RECORDS] (1012)
164 161 use cctr [CENTRAL UNIQUE RECORDS] (72)

APPENDIX 3: LIST OF INCLUDED STUDIES (SYSTEMATIC REVIEW)

1. Akyol Y, Tander B, Alayli G*, et al.* The comparison of effectiveness of alendronate and risedronate in osteoporosis treatment. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi. 2006; 52(3):110-4.
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APPENDIX 4: LIST OF EXCLUDED FULL-TEXT RECORDS (SYSTEMATIC REVIEW)

Excluded due to population (N=10 studies)

1. Barone A, Giusti A, Pioli G*, et al.* Secondary hyperparathyroidism due to hypovitaminosis D affects bone mineral density response to alendronate in elderly women with osteoporosis: A randomized controlled trial. J Am Geriatr Soc. 2007; 55(5):752-7.
2. Carlino G, Cozzolongo A. Effects of intravenous zoledronic acid following subcutaneous teriparatide in postmenopausal osteoporosis. Bone. 2011; 48(Suppl 2):S220.
3. Cesareo R, Di SE, Vescini F*, et al.* Effects of alendronate and vitamin D in patients with normocalcemic primary hyperparathyroidism. Osteoporos Int. 2015; 26 (4):1295-302.
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6. Ikeda T, Manabe H, Iwata K. Clinical significance of alendronate in postmenopausal type 2 diabetes mellitus. Diabetes Metab. 2004; 30(4):355-8.
7. McComsey GA, Kendall MA, Tebas P*, et al.* Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. AIDS (London, England). 2007; 21:2473-82.
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9. Sato Y, Iwamoto J, Kanoko T, Satoh K. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: A randomized controlled trial. Mov Disord. 2006; 21(7):924-9.
10. Unnanuntana A, Jarusriwanna A, Songcharoen P. Randomized clinical trial comparing efficacy and safety of brand versus generic alendronate (Bonmax®) for osteoporosis treatment. PLoS One. 2017; 12(7):e0180325.

Excluded due to intervention or comparator (N=15 studies)

1. Caffarelli C, Gonnelli S, Tanzilli L*, et al.* Apparent bone mineral density at femoral neck in the monitoring the early effects of teriparatide. Bone. 2010; 47(Suppl 1):S203-S4.
2. Galesanu C, Florescu A, Iulia LA*, et al.* Effects of combined treatment with alendronate and alfacalcidol comparing with other bisphosphonates and alfacalcidol in BMD changes at postmenopausal osteoporotic women. J Bone Miner Res. 2012; 27(Suppl 1). Available at http://www.asbmr.org/education/AbstractDetail?aid=f7671a87-84df-43fd-b4cf-9797a36150fa.
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Excluded due to less than one year of treatment (N=51 studies)

1. Adachi JD, Faraawi RY, O'Mahony MF*, et al.* Upper gastrointestinal tolerability of alendronate sodium monohydrate 10 mg once daily in postmenopausal women: A 12-week, randomized, double-blind, placebo-controlled, exploratory study. Clin Ther. 2009; 31(8):1747-53.
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Excluded due to study type or design (N=32 studies)

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Excluded due not reporting relevant outcome data (N=139 studies)

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Excluded due to duplication with other records (N=12 studies)

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Awaiting full-text for assessment (N=1 study)

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APPENDIX 5: LIST OF INCLUDED STUDIES (NETWORK META-ANALYSIS)

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APPENDIX 6: LIST OF EXCLUDED FULL-TEXT RECORDS (NETWORK META-ANALYSIS)

Excluded due to population (N=21 studies)

1. Aro H, Moritz N, Timlin S, *et al.* A single dose of an intravenous bisphosphonate prevents periprosthetic bone loss but does not enhance RSA-evaluated osseointegration of uncemented femoral stems. Hip Int. 2012; 22(Suppl 1):443.
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Excluded due to duplication with other records (N=17 studies)

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Awaiting full-text for assessment (N=3 studies)

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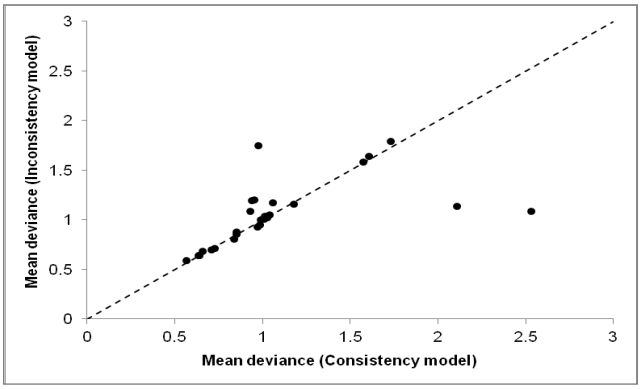
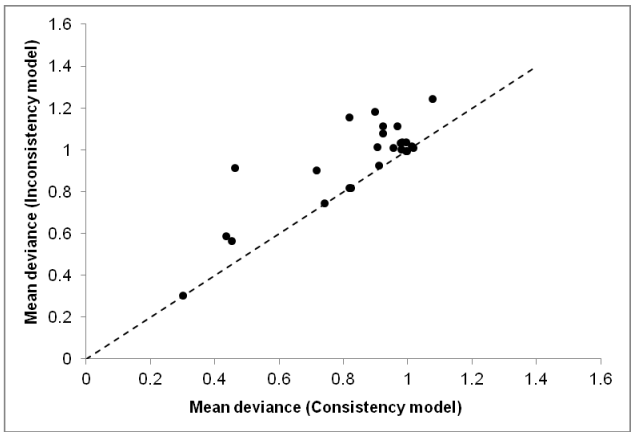
APPENDIX 7: INCONSISTENCY PLOTS

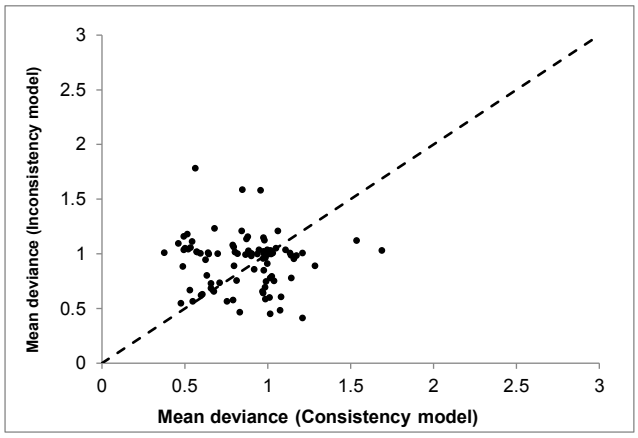
Inconsistency plot for radiographic vertebral fractures



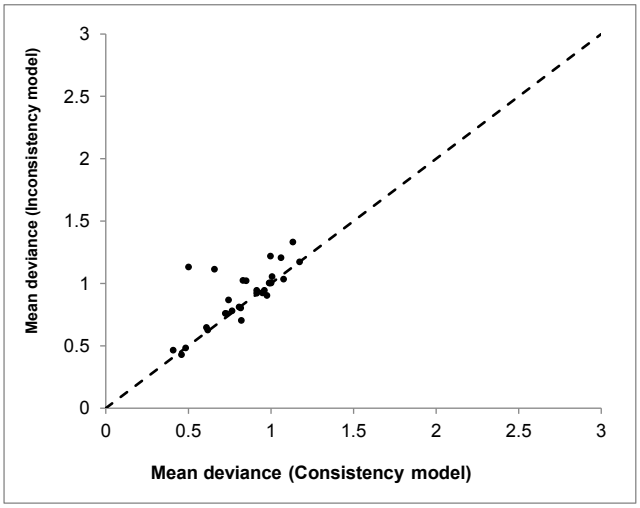
Inconsistency plot for clinical vertebral fractures



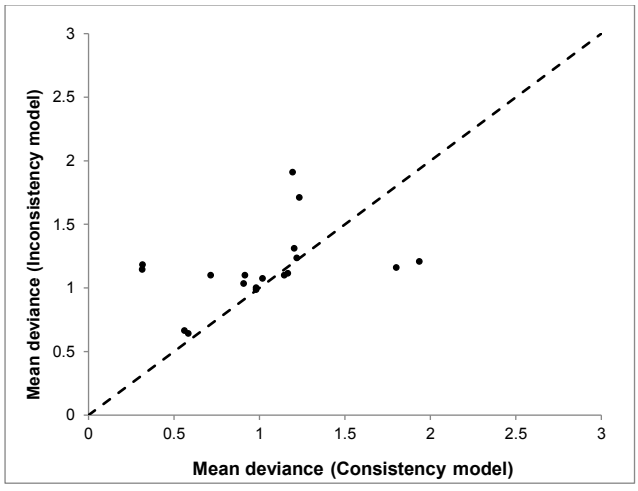
Inconsistency plot for non-vertebral fractures



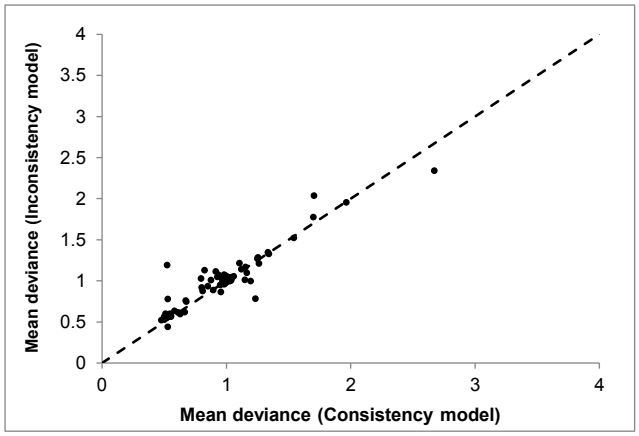
Inconsistency plot for hip fractures



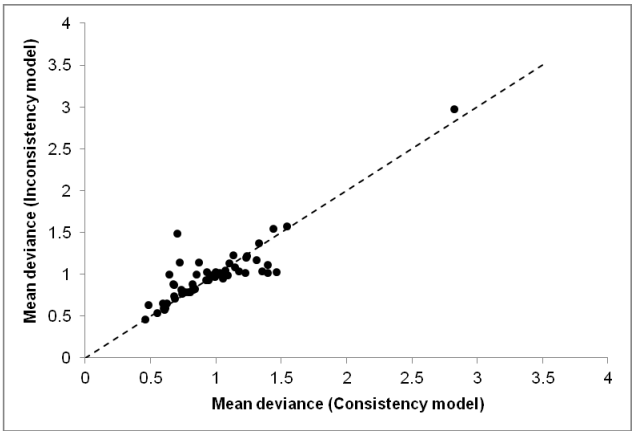
Inconsistency plot for wrist fractures



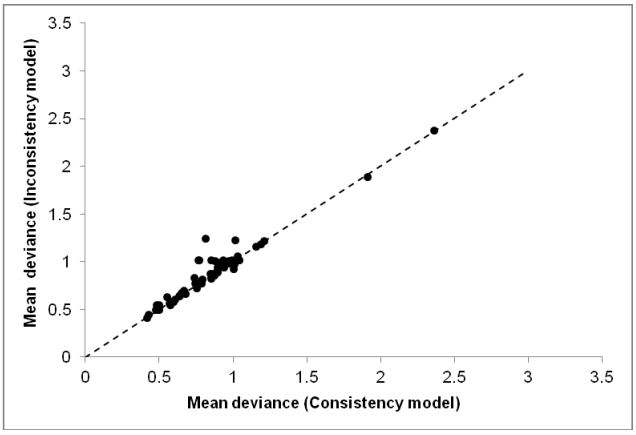
Inconsistency plot for withdrawal due to adverse events

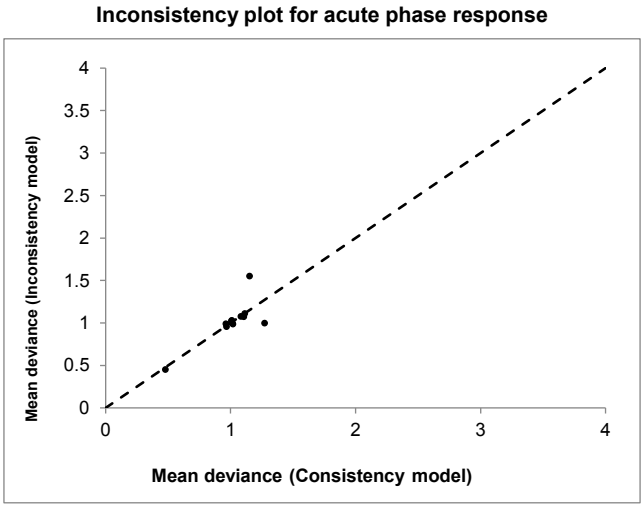


Inconsistency plot for serious adverse events



Inconsistency plot for gastrointestinal adverse events





APPENDIX 8: INVESTIGATION OF NETWORK INCONSISTENCY

Main analysis of radiographic vertebral fracture

Within the loop formed by placebo, risedronate 2.5 mg/day and etidronate 200 mg/day, direct evidence from a two-arm study was inconsistent (Figure 8.1). Five trials in the closed loop are described in Table 8.1. The inconsistent study provided the only link between 2 studies evaluating placebo and etidronate 200 mg/day and 2 trials comparing placebo to risedronate 2.5 mg/day. Fracture data indicates etidronate is more effective than placebo and risedronate is similar to placebo. However, the inconsistent study shows risedronate as more effective than etidronate, which may be a source of loop inconsistency. Potential reasons for the inconsistency are the inclusion of men within the trial and short treatment duration compared to other studies. Two men were included in the risedronate group while all other studies included women only. Since only 2 fractures occurred during the trial, both in the etidronate group, it is possible that the lower fracture rate observed in the risedronate group may be caused by the inclusion of fewer women. Also, the study lasted 48 weeks whereas other studies lasted one to two years. Since estimates are based on few events, a longer duration may have captured more events which would change the distribution of fractures among intervention groups. In a sensitivity analysis where the inconsistent study was removed, etidronate 200 mg/day showed significantly greater efficacy than risedronate for fracture prevention (OR 0.21, 95% CrI: 0.06, 0.76). Etidronate remained significantly better than placebo as in the main analysis, but the sensitivity results showed greater efficacy and precision (main OR 0.31, 95% CrI: 0.13, 0.68; sensitivity OR 0.22, 95% CrI: 0.09, 0.53). Risedronate 2.5 mg/day remained worse than placebo as in the main analysis, but the sensitivity results showed lower efficacy and precision (main OR 0.75, 95% CrI: 0.29, 1.55; sensitivity OR 1.08, 95% CrI: 0.44, 2.51). Etidronate 200 mg/day also showed greater efficacy than alendronate 10 mg/day, whereas previously the effect estimate was suggestive but not statistically significant. Risedronate became significantly worse than zoledronic acid 5 mg/year, and minodronate 1 mg/day whereas previously this was suggested but not significant. The credible intervals for most of other interventions did not change significantly, and any changes in significance are due to narrowing of intervals and not changes in effect estimates themselves, nor did any change in direction occur. Results are presented in Table 6.4.

Figure 8.1: Network diagram for radiographic vertebral fractures

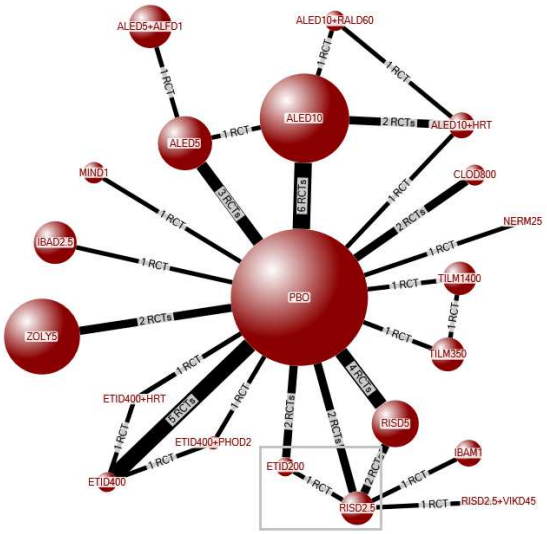


Table 8.1: Studies in the loop formed by placebo, risedronate 2.5 mg/d and etidronate 200 mg/d.

Study	Type	Interventions	Raw fracture data		Treatment duration	Age (yr), mean (SD)	LS T-score	Baseline vertebral fracture	Population
Fukunaga 2002	Secondary	ETI 200 mg/d **RIS 2.5 mg/d**	2/107 0/102	2% 0%	48 weeks	62.6 (6.2)	-3.0 (1.0)	14%	Age 40–75 yrs, ambulatory women or men, involutional osteoporosis, LS BMD <70% of YAM without vertebral fracture, or <80% of YAM with vertebral fractures.
Ishida 2004	Secondary	Placebo **ETI 200 mg/d**	17/66 8/66	26% 12%	2 years	46.2 (14.2)	-	31%	Age < 75 yrs, postmenopausal ≥ 5 yrs, osteoporosis (BMD 30% below YAM or BMD 20% below YAM and 1vertebral fracture).
Shiota 2001	Secondary	Placebo **ETI 200 mg/d**	11/20 1/20	55% 5%	2 years	61.7 (6.7)	-	-	Age > 50 yrs, postmenopausal, visited outpatient clinic due to lumbo-dorsal pain.
Mortensen 1998	Primary	**Placebo** RIS 2.5 mg/d	0/36 1/38	0% 3%	1 year	51.5 (3.8)	-	0%	LS BMD within 2 SD of mean bone mass, postmenopausal 6 to 60 mo, ambulatory, active, weigh between 45-90 kg, within 25% of normal BMI.
Fogelman 2000	Secondary	Placebo **RIS 2.5 mg/d**	17/125 8/60	14% 13%	2 years	64.7 (7.2)	-2.9 (1.8)	29%	Age <80 yrs, postmenopausal ≥ 1 yr, mean LS T-score of <-2.

*ETI=etidronate, RIS=risedronate. Bolded studies indicate lower fracture rate within the same comparison.

Table 8.2: Sensitivity analysis for radiographic vertebral fracture excluding inconsistent study (Fukunaga et al., 2002)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
ALED5	PBO	0.54 (0.31,0.93)	0.54 (0.31,0.92)
ALED5+ALFD1		0.49 (0.23,1.05)	0.49 (0.24,1.02)
ALED10		0.58 (0.44,0.76)	0.58 (0.44,0.76)
ALED10+HRT		0.61 (0.19,2.30)	0.64 (0.17,2.28)
ALED10+RALD60		0.15 (0.01,1.19)	0.15 (0.01,0.94)
ETID200		0.31 (0.13,0.68)	0.22 (0.09,0.53)
ETID400		0.44 (0.21,0.89)	0.45 (0.22,0.89)
ETID400+HRT		0.10 (0.005,0.71)	0.11 (0.003,0.75)
ETID400+PHOD2		0.24 (0.05,0.80)	0.23 (0.06,0.86)
RISD2.5		0.75 (0.29,1.55)	1.08 (0.44,2.51)
RISD2.5+VIKD45		1.12 (0.19,6.85)	1.47 (0.23,10.42)
RISD5		0.53 (0.38,0.73)	0.54 (0.39,0.75)
IBAD2.5		0.49 (0.28,0.84)	0.48 (0.27,0.82)
IBAM1		0.63 (0.21,1.57)	0.91 (0.32,2.52)
ZOLY5		0.27 (0.18,0.43)	0.27 (0.18,0.44)
MIND1		0.19 (0.05,0.56)	0.18 (0.05,0.56)
CLOD800		0.63 (0.33,1.20)	0.63 (0.34,1.19)
NERM25		0.26 (0.02,2.66)	0.24 (0.01,1.87)
TILM350		1.11 (0.69,1.77)	1.11 (0.69,1.79)
TILM1400		1.02 (0.63,1.61)	1.02 (0.62,1.64)
ALED5+ALFD1	ALED5	0.91 (0.55,1.52)	0.91 (0.54,1.51)

ALED10		1.08 (0.59,1.94)	1.07 (0.60,1.94)
ALED10+HRT		1.13 (0.31,4.69)	1.17 (0.26,4.87)
ALED10+RALD60		0.28 (0.02,2.53)	0.28 (0.02,1.87)
ETID200		0.57 (0.22,1.49)	0.41 (0.14,1.16)
ETID400		0.82 (0.33,2.01)	0.85 (0.34,2.03)
ETID400+HRT		0.19 (0.01,1.50)	0.20 (0.01,1.58)
ETID400+PHOD2		0.45 (0.09,1.63)	0.43 (0.10,1.79)
RISD2.5		1.39 (0.48,3.42)	2.01 (0.69,5.29)
RISD2.5+VIKD45		2.06 (0.32,13.33)	2.72 (0.39,21.04)
RISD5		0.98 (0.51,1.86)	0.99 (0.53,1.89)
IBAD2.5		0.91 (0.42,1.94)	0.89 (0.41,1.93)
IBAM1		1.19 (0.34,3.35)	1.71 (0.51,5.29)
ZOLY5		0.50 (0.26,1.02)	0.50 (0.26,1.02)
MIND1		0.35 (0.08,1.21)	0.34 (0.08,1.17)
CLOD800		1.17 (0.50,2.70)	1.16 (0.51,2.75)
NERM25		0.48 (0.03,5.62)	0.45 (0.02,3.71)
TILM350		2.06 (0.99,4.18)	2.07 (1.01,4.15)
TILM1400		1.89 (0.89,3.85)	1.89 (0.93,3.81)
ALED10	ALED5+ALFD1	1.19 (0.53,2.53)	1.19 (0.55,2.53)
ALED10+HRT		1.25 (0.31,5.64)	1.29 (0.27,5.84)
ALED10+RALD60		0.31 (0.02,2.93)	0.30 (0.02,2.21)
ETID200		0.64 (0.21,1.82)	0.45 (0.13,1.41)
ETID400		0.89 (0.31,2.52)	0.93 (0.33,2.54)
ETID400+HRT		0.21 (0.01,1.80)	0.22 (0.01,1.80)
ETID400+PHOD2		0.50 (0.08,1.96)	0.48 (0.10,2.14)
RISD2.5		1.53 (0.46,4.27)	2.21 (0.67,6.53)
RISD2.5+VIKD45		2.26 (0.33,15.38)	2.97 (0.40,24.16)
RISD5		1.09 (0.47,2.39)	1.10 (0.49,2.44)
IBAD2.5		1.00 (0.39,2.46)	0.98 (0.39,2.45)
IBAM1		1.29 (0.34,4.07)	1.86 (0.50,6.45)
ZOLY5		0.55 (0.24,1.31)	0.55 (0.24,1.35)
MIND1		0.38 (0.08,1.46)	0.38 (0.08,1.41)
CLOD800		1.29 (0.48,3.37)	1.28 (0.49,3.51)
NERM25		0.53 (0.03,6.24)	0.49 (0.02,4.17)
TILM350		2.28 (0.92,5.38)	2.29 (0.95,5.34)
TILM1400		2.08 (0.83,4.92)	2.08 (0.86,4.90)
ALED10+HRT	ALED10	1.07 (0.32,3.95)	1.10 (0.29,3.94)
ALED10+RALD60		0.27 (0.01,2.07)	0.27 (0.02,1.60)
ETID200		0.53 (0.22,1.24)	0.39 (0.14,0.95)
ETID400		0.76 (0.35,1.65)	0.78 (0.36,1.64)
ETID400+HRT		0.18 (0.01,1.26)	0.19 (0.01,1.35)
ETID400+PHOD2		0.42 (0.08,1.44)	0.40 (0.10,1.55)
RISD2.5		1.29 (0.49,2.82)	1.86 (0.74,4.50)
RISD2.5+VIKD45		1.95 (0.31,12.26)	2.52 (0.39,18.04)
RISD5		0.91 (0.59,1.39)	0.93 (0.60,1.42)
IBAD2.5		0.84 (0.45,1.54)	0.83 (0.44,1.52)
IBAM1		1.09 (0.35,2.81)	1.58 (0.54,4.50)
ZOLY5		0.46 (0.29,0.80)	0.46 (0.29,0.81)
MIND1		0.33 (0.08,1.03)	0.32 (0.09,0.99)
CLOD800		1.09 (0.54,2.17)	1.09 (0.55,2.15)
NERM25		0.45 (0.03,4.69)	0.42 (0.02,3.27)
TILM350		1.92 (1.12,3.27)	1.93 (1.12,3.29)
TILM1400		1.75 (1.00,2.99)	1.76 (1.01,3.02)
ALED10+RALD60	ALED10+HRT	0.24 (0.01,1.77)	0.24 (0.02,1.63)
ETID200		0.51 (0.11,2.05)	0.34 (0.08,1.60)
ETID400		0.73 (0.16,2.66)	0.72 (0.17,3.05)
ETID400+HRT		0.16 (0.01,1.62)	0.16 (0.004,1.93)
ETID400+PHOD2		0.40 (0.04,2.33)	0.37 (0.05,2.35)
RISD2.5		1.18 (0.24,5.04)	1.67 (0.39,8.07)
RISD2.5+VIKD45		1.83 (0.17,15.55)	2.34 (0.24,22.42)
RISD5		0.86 (0.22,2.97)	0.84 (0.23,3.35)
IBAD2.5		0.79 (0.19,3.05)	0.76 (0.19,3.24)
IBAM1		1.00 (0.18,4.85)	1.42 (0.30,7.55)
ZOLY5		0.45 (0.11,1.61)	0.43 (0.11,1.76)
MIND1		0.30 (0.04,1.68)	0.28 (0.05,1.73)
CLOD800		1.01 (0.23,4.07)	0.99 (0.25,4.39)
NERM25		0.41 (0.02,5.14)	0.38 (0.02,4.62)
TILM350		1.81 (0.46,6.44)	1.74 (0.45,7.09)
TILM1400		1.66 (0.41,5.90)	1.58 (0.41,6.53)
ETID200	ALED10+RALD60	2.00 (0.23,35.51)	1.49 (0.19,27.55)
ETID400		2.97 (0.32,52.54)	2.98 (0.41,55.49)
ETID400+HRT		0.65 (0.02,22.52)	0.67 (0.01,23.12)
ETID400+PHOD2		1.64 (0.10,35.98)	1.63 (0.15,32.17)
RISD2.5		4.80 (0.50,99.65)	7.03 (1.05,118.90)
RISD2.5+VIKD45		7.77 (0.46,233.10)	9.86 (0.71,278.40)
RISD5		3.40 (0.44,64.67)	3.54 (0.55,59.86)
IBAD2.5		3.22 (0.38,58.62)	3.17 (0.47,53.82)
IBAM1		4.11 (0.39,93.75)	5.99 (0.80,111.90)
ZOLY5		1.76 (0.22,32.75)	1.79 (0.28,31.54)
MIND1		1.23 (0.11,24.92)	1.20 (0.13,24.24)

CLOD800		4.16 (0.47,81.53)	4.20 (0.59,77.44)
NERM25		1.87 (0.05,45.24)	1.54 (0.04,47.20)
TILM350		7.22 (0.88,136.90)	7.29 (1.12,134.10)
TILM1400		6.56 (0.80,129.10)	6.66 (1.02,118.70)
ETID400	ETID200	1.42 (0.47,4.16)	2.03 (0.66,6.56)
ETID400+HRT		0.33 (0.01,2.74)	0.47 (0.01,4.53)
ETID400+PHOD2		0.78 (0.13,3.32)	1.06 (0.19,5.52)
RISD2.5		2.36 (0.78,6.94)	4.86 (1.32,17.81)
RISD2.5+VIKD45		3.56 (0.58,25.08)	6.76 (0.83,59.96)
RISD5		1.72 (0.71,4.11)	2.38 (0.95,6.67)
IBAD2.5		1.58 (0.60,4.25)	2.18 (0.77,6.36)
IBAM1		2.01 (0.58,6.60)	4.13 (0.98,16.85)
ZOLY5		0.88 (0.37,2.25)	1.21 (0.47,3.53)
MIND1		0.60 (0.12,2.42)	0.83 (0.17,3.54)
CLOD800		2.04 (0.70,5.88)	2.85 (0.93,9.02)
NERM25		0.83 (0.05,10.47)	1.09 (0.04,10.19)
TILM350		3.61 (1.40,9.18)	4.98 (1.85,14.50)
TILM1400		3.29 (1.28,8.45)	4.56 (1.69,13.21)
ETID400+HRT	ETID400	0.23 (0.01,1.79)	0.23 (0.01,1.82)
ETID400+PHOD2		0.55 (0.12,1.99)	0.53 (0.12,1.87)
RISD2.5		1.67 (0.54,4.94)	2.39 (0.76,7.52)
RISD2.5+VIKD45		2.58 (0.36,17.94)	3.32 (0.44,27.79)
RISD5		1.20 (0.55,2.73)	1.19 (0.56,2.64)
IBAD2.5		1.11 (0.45,2.74)	1.07 (0.45,2.62)
IBAM1		1.41 (0.40,4.77)	2.01 (0.56,7.35)
ZOLY5		0.61 (0.28,1.44)	0.60 (0.27,1.39)
MIND1		0.43 (0.09,1.52)	0.41 (0.10,1.53)
CLOD800		1.44 (0.54,3.73)	1.38 (0.56,3.67)
NERM25		0.60 (0.03,7.16)	0.52 (0.03,4.32)
TILM350		2.50 (1.08,5.88)	2.46 (1.09,5.82)
TILM1400		2.31 (0.98,5.37)	2.25 (0.98,5.34)
ETID400+PHOD2	ETID400+HRT	2.30 (0.21,80.52)	2.18 (0.19,91.72)
RISD2.5		7.15 (0.79,174.80)	10.04 (1.16,364.20)
RISD2.5+VIKD45		11.39 (0.54,364.20)	14.57 (0.84,570.20)
RISD5		5.07 (0.73,110.30)	5.02 (0.69,155.80)
IBAD2.5		4.76 (0.61,107.60)	4.44 (0.59,143.50)
IBAM1		6.05 (0.64,148.90)	8.63 (0.90,327.90)
ZOLY5		2.62 (0.36,57.26)	2.49 (0.33,85.15)
MIND1		1.86 (0.17,46.32)	1.82 (0.17,65.06)
CLOD800		6.03 (0.80,130.80)	5.87 (0.73,198.40)
NERM25		2.74 (0.06,109.70)	2.42 (0.05,100.90)
TILM350		10.58 (1.47,237.90)	10.22 (1.39,344.00)
TILM1400		9.67 (1.35,224.30)	9.28 (1.28,308.80)
RISD2.5	ETID400+PHOD2	3.08 (0.62,16.66)	4.60 (0.96,25.11)
RISD2.5+VIKD45		4.71 (0.52,45.30)	6.15 (0.67,74.49)
RISD5		2.16 (0.62,11.07)	2.29 (0.61,9.64)
IBAD2.5		2.00 (0.53,10.61)	2.07 (0.50,9.25)
IBAM1		2.65 (0.47,15.25)	3.89 (0.74,23.20)
ZOLY5		1.11 (0.31,5.70)	1.15 (0.30,5.14)
MIND1		0.75 (0.14,5.17)	0.79 (0.13,4.59)
CLOD800		2.58 (0.67,14.09)	2.68 (0.65,12.67)
NERM25		1.08 (0.05,19.57)	0.92 (0.05,12.54)
TILM350		4.54 (1.25,23.51)	4.80 (1.18,20.30)
TILM1400		4.13 (1.16,21.94)	4.38 (1.07,18.69)
RISD2.5+VIKD45	RISD2.5	1.55 (0.29,7.71)	1.39 (0.25,7.98)
RISD5		0.71 (0.33,1.81)	0.49 (0.21,1.26)
IBAD2.5		0.65 (0.26,1.94)	0.45 (0.17,1.25)
IBAM1		0.84 (0.48,1.51)	0.85 (0.48,1.51)
ZOLY5		0.36 (0.16,1.03)	0.25 (0.10,0.69)
MIND1		0.25 (0.06,1.04)	0.17 (0.04,0.71)
CLOD800		0.84 (0.32,2.59)	0.58 (0.21,1.72)
NERM25		0.35 (0.02,4.45)	0.22 (0.01,2.15)
TILM350		1.48 (0.62,4.16)	1.04 (0.40,2.84)
TILM1400		1.35 (0.57,3.84)	0.94 (0.36,2.58)
RISD5	RISD2.5+VIKD45	0.47 (0.08,2.90)	0.36 (0.05,2.44)
IBAD2.5		0.44 (0.06,2.79)	0.33 (0.04,2.37)
IBAM1		0.54 (0.10,3.11)	0.61 (0.10,3.71)
ZOLY5		0.24 (0.04,1.58)	0.18 (0.03,1.30)
MIND1		0.17 (0.02,1.40)	0.12 (0.01,1.08)
CLOD800		0.55 (0.08,3.94)	0.43 (0.05,3.01)
NERM25		0.23 (0.01,4.48)	0.16 (0.004,2.35)
TILM350		0.98 (0.15,6.20)	0.76 (0.10,5.20)
TILM1400		0.90 (0.14,5.63)	0.69 (0.09,4.72)
IBAD2.5	RISD5	0.92 (0.49,1.76)	0.89 (0.47,1.70)
IBAM1		1.20 (0.39,3.04)	1.71 (0.58,4.80)
ZOLY5		0.51 (0.31,0.92)	0.50 (0.31,0.91)
MIND1		0.36 (0.09,1.16)	0.34 (0.09,1.08)
CLOD800		1.19 (0.58,2.50)	1.18 (0.58,2.39)
NERM25		0.50 (0.03,5.10)	0.45 (0.02,3.53)
TILM350		2.10 (1.18,3.71)	2.07 (1.17,3.68)

TILM1400		1.93 (1.07,3.41)	1.89 (1.06,3.37)
IBAM1	IBAD2.5	1.30 (0.38,3.79)	1.90 (0.59,5.98)
ZOLY5		0.55 (0.29,1.14)	0.56 (0.30,1.19)
MIND1		0.39 (0.09,1.34)	0.38 (0.09,1.31)
CLOD800		1.28 (0.56,3.05)	1.31 (0.58,3.11)
NERM25		0.53 (0.03,5.63)	0.50 (0.02,4.07)
TILM350		2.27 (1.11,4.64)	2.32 (1.14,4.82)
TILM1400		2.08 (1.00,4.27)	2.12 (1.03,4.44)
ZOLY5	IBAM1	0.43 (0.16,1.43)	0.29 (0.10,0.96)
MIND1		0.29 (0.06,1.35)	0.20 (0.04,0.93)
CLOD800		0.99 (0.33,3.57)	0.69 (0.22,2.32)
NERM25		0.41 (0.02,5.78)	0.26 (0.01,2.64)
TILM350		1.75 (0.63,5.73)	1.23 (0.40,3.81)
TILM1400		1.60 (0.58,5.23)	1.11 (0.37,3.48)
MIND1	ZOLY5	0.69 (0.17,2.24)	0.68 (0.18,2.20)
CLOD800		2.31 (1.07,4.95)	2.34 (1.08,4.83)
NERM25		0.97 (0.06,10.11)	0.89 (0.04,7.24)
TILM350		4.13 (2.08,7.38)	4.16 (2.05,7.44)
TILM1400		3.79 (1.89,6.75)	3.80 (1.87,6.75)
CLOD800	MIND1	3.36 (0.94,14.80)	3.42 (0.95,14.50)
NERM25		1.43 (0.07,18.85)	1.27 (0.05,14.51)
TILM350		5.88 (1.80,24.44)	6.09 (1.82,23.85)
TILM1400		5.38 (1.64,21.94)	5.52 (1.66,22.16)
NERM25	CLOD800	0.41 (0.02,4.57)	0.39 (0.02,3.10)
TILM350		1.77 (0.79,3.88)	1.76 (0.81,3.81)
TILM1400		1.62 (0.72,3.53)	1.62 (0.72,3.48)
TILM350	NERM25	4.24 (0.40,69.26)	4.68 (0.57,110.40)
TILM1400		3.90 (0.36,62.76)	4.26 (0.52,101.40)
TILM1400	TILM350	0.92 (0.57,1.46)	0.91 (0.57,1.46)

Subgroup analysis of secondary prevention studies

The study by Fukunaga et al. (2002) was also found to be inconsistent with other studies within the closed loop of a subgroup analysis of secondary prevention studies (Figure 8.2). Since most studies from the main analysis are secondary prevention trials, the same closed loop between placebo, etidronate and risedronate overlap in the main and subgroup analyses. Thus, potential reasons of inconsistency are also assumed to be similar (Table 8.3). When the study was excluded as a sensitivity analysis we saw an increase in the efficacy of etidronate 200 mg/day compared to risedronate 2.5 mg/day, and greater efficacy of other doses of etidronate as well as a lower efficacy of other doses of risedronate. Results of the analysis are shown in Table 8.4.

Figure 8.2: Network diagram for radiographic vertebral fractures (secondary prevention)

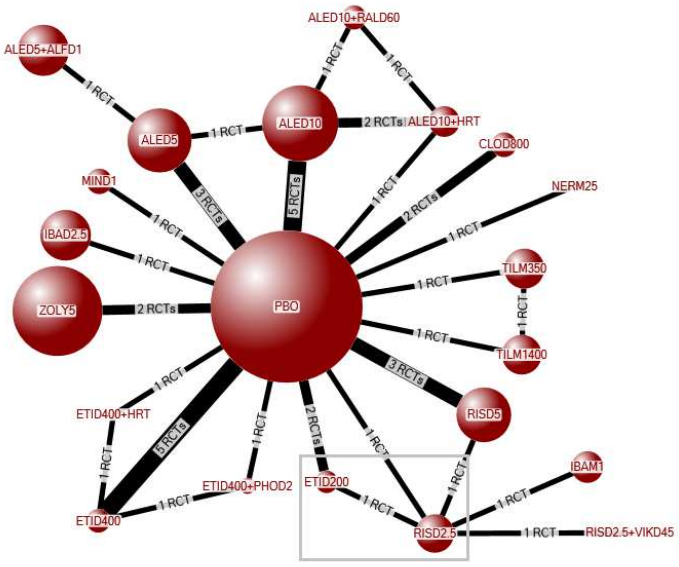


Table 8.3: Studies in the loop formed by placebo, risedronate 2.5 mg/d and etidronate 200 mg/d.

Study	Type	Interventions	Raw fracture data		Treatment duration	Age (yr), mean (SD)	LS T-score	Baseline vertebral fracture	Population
Fukunaga 2002	Secondary	ETI 200 mg/d **RIS 2.5 mg/d**	2/107 0/102	2% 0%	48 weeks	62.6 (6.2)	-3.0 (1.0)	14%	Age 40–75 yrs, ambulatory women or men, involutional osteoporosis, LS BMD <70% of YAM without vertebral fracture, or <80% of YAM with vertebral fractures.
Ishida 2004	Secondary	Placebo **ETI 200 mg/d**	17/66 8/66	26% 12%	2 years	46.2 (14.2)	-	31%	Age < 75 yrs, postmenopausal ≥ 5 yrs, osteoporosis (BMD 30% below YAM or BMD 20% below YAM and 1vertebral fracture).
Shiota 2001	Secondary	Placebo **ETI 200 mg/d**	11/20 1/20	55% 5%	2 years	61.7 (6.7)	-	-	Age > 50 yrs, postmenopausal, visited outpatient clinic due to lumbo-dorsal pain.
Fogelman 2000	Secondary	Placebo **RIS 2.5 mg/d**	17/125 8/60	14% 13%	2 years	64.7 (7.2)	-2.9 (1.8)	29%	Age <80 yrs, postmenopausal ≥ 1 yr, mean LS T-score of <-2.

*ETI=etidronate, RIS=risedronate. Bolded studies indicate lower fracture rate within the same comparison.

Table 8.4: Results of the sensitivity analysis for radiographic vertebral fracture (subgroup analysis, secondary prevention) excluding inconsistent study (Fukunaga et al., 2002)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
ALED5	PBO	0.56 (0.31,0.94)	0.55 (0.31,0.93)
ALED5+ALFD1		0.51 (0.22,1.11)	0.50 (0.23,1.08)
ALED10		0.59 (0.42,0.83)	0.59 (0.42,0.82)
ALED10+HRT		0.63 (0.17,2.18)	0.62 (0.19,2.21)
ALED10+RALD60		0.16 (0.01,0.98)	0.15 (0.01,1.04)
ETID200		0.31 (0.13,0.70)	0.22 (0.09,0.52)
ETID400		0.45 (0.23,0.87)	0.45 (0.22,0.88)
ETID400+HRT		0.13 (0.01,0.82)	0.10 (0.01,0.67)
ETID400+PHOD2		0.25 (0.06,0.88)	0.24 (0.05,0.81)
RISD2.5		0.68 (0.23,1.67)	1.00 (0.36,2.45)
RISD2.5+VIKD45		0.99 (0.15,7.27)	1.48 (0.23,9.41)
RISD5		0.53 (0.36,0.75)	0.54 (0.37,0.77)
IBAD2.5		0.48 (0.26,0.88)	0.48 (0.27,0.87)
IBAM1		0.45 (0.21,0.93)	0.46 (0.22,0.93)
ZOLY5		0.27 (0.18,0.47)	0.27 (0.18,0.46)
MIND1		0.18 (0.05,0.57)	0.18 (0.05,0.56)
CLOD800		0.64 (0.33,1.30)	0.62 (0.32,1.25)
NERM25		0.23 (0.01,2.44)	0.28 (0.01,2.13)
TILM350		1.11 (0.65,1.89)	1.11 (0.66,1.87)
TILM1400		1.02 (0.59,1.72)	1.01 (0.60,1.72)
ALED5+ALFD1	ALED5	0.92 (0.52,1.63)	0.91 (0.53,1.58)
ALED10		1.07 (0.57,2.06)	1.07 (0.58,2.05)
ALED10+HRT		1.14 (0.29,4.23)	1.12 (0.31,4.68)
ALED10+RALD60		0.29 (0.01,2.04)	0.26 (0.01,2.13)
ETID200		0.55 (0.21,1.58)	0.41 (0.14,1.12)
ETID400		0.82 (0.34,1.99)	0.82 (0.33,1.98)
ETID400+HRT		0.23 (0.01,1.64)	0.17 (0.01,1.37)
ETID400+PHOD2		0.46 (0.10,1.80)	0.43 (0.09,1.75)
RISD2.5		1.23 (0.35,3.68)	1.81 (0.58,5.46)
RISD2.5+VIKD45		1.78 (0.25,14.30)	2.70 (0.38,19.18)
RISD5		0.96 (0.49,1.90)	0.97 (0.51,1.93)
IBAD2.5		0.87 (0.39,2.00)	0.88 (0.40,2.01)
IBAM1		0.82 (0.32,2.07)	0.83 (0.34,2.05)
ZOLY5		0.49 (0.25,1.08)	0.49 (0.25,1.08)
MIND1		0.33 (0.08,1.18)	0.33 (0.08,1.17)
CLOD800		1.15 (0.49,2.92)	1.13 (0.51,2.77)
NERM25		0.43 (0.02,4.54)	0.50 (0.02,4.01)
TILM350		1.99 (0.94,4.47)	2.01 (0.97,4.43)
TILM1400		1.83 (0.85,4.10)	1.85 (0.88,4.08)
ALED10	ALED5+ALFD1	1.17 (0.50,2.73)	1.17 (0.51,2.71)
ALED10+HRT		1.24 (0.28,5.04)	1.22 (0.30,5.72)
ALED10+RALD60		0.31 (0.02,2.44)	0.29 (0.02,2.53)
ETID200		0.61 (0.20,1.92)	0.45 (0.13,1.39)
ETID400		0.89 (0.31,2.54)	0.90 (0.30,2.57)
ETID400+HRT		0.25 (0.02,1.88)	0.19 (0.01,1.61)
ETID400+PHOD2		0.50 (0.10,2.14)	0.46 (0.09,2.13)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
RISD2.5		1.34 (0.34,4.49)	1.96 (0.56,6.82)
RISD2.5+VIKD45		1.94 (0.26,17.37)	2.93 (0.39,22.86)
RISD5		1.05 (0.44,2.52)	1.07 (0.46,2.56)
IBAD2.5		0.95 (0.35,2.62)	0.96 (0.37,2.57)
IBAM1		0.90 (0.30,2.62)	0.91 (0.32,2.60)
ZOLY5		0.54 (0.22,1.46)	0.54 (0.23,1.41)
MIND1		0.36 (0.08,1.45)	0.36 (0.08,1.48)
CLOD800		1.25 (0.46,3.74)	1.24 (0.48,3.54)
NERM25		0.46 (0.02,5.37)	0.54 (0.02,4.69)
TILM350		2.19 (0.84,5.88)	2.21 (0.89,5.68)
TILM1400		2.00 (0.77,5.27)	2.02 (0.80,5.23)
ALED10+HRT	ALED10	1.06 (0.30,3.59)	1.05 (0.32,3.69)
ALED10+RALD60		0.27 (0.01,1.67)	0.25 (0.02,1.73)
ETID200		0.52 (0.21,1.25)	0.38 (0.14,0.92)
ETID400		0.77 (0.36,1.57)	0.76 (0.35,1.61)
ETID400+HRT		0.22 (0.01,1.43)	0.16 (0.01,1.19)
ETID400+PHOD2		0.43 (0.09,1.58)	0.41 (0.08,1.43)
RISD2.5		1.15 (0.38,2.98)	1.69 (0.58,4.42)
RISD2.5+VIKD45		1.68 (0.24,12.65)	2.51 (0.38,16.44)
RISD5		0.90 (0.53,1.45)	0.92 (0.56,1.48)
IBAD2.5		0.82 (0.41,1.62)	0.83 (0.42,1.60)
IBAM1		0.77 (0.34,1.70)	0.77 (0.35,1.70)
ZOLY5		0.46 (0.27,0.88)	0.46 (0.28,0.86)
MIND1		0.31 (0.08,0.99)	0.32 (0.08,1.00)
CLOD800		1.08 (0.51,2.35)	1.06 (0.51,2.31)
NERM25		0.40 (0.02,4.18)	0.47 (0.02,3.72)
TILM350		1.88 (0.98,3.49)	1.89 (1.02,3.50)
TILM1400		1.72 (0.90,3.22)	1.74 (0.93,3.19)
ALED10+RALD60	ALED10+HRT	0.26 (0.01,1.64)	0.24 (0.02,1.59)
ETID200		0.49 (0.12,2.21)	0.36 (0.08,1.48)
ETID400		0.71 (0.18,3.07)	0.72 (0.17,3.17)
ETID400+HRT		0.20 (0.01,2.21)	0.16 (0.01,1.69)
ETID400+PHOD2		0.41 (0.06,2.24)	0.38 (0.05,2.03)
RISD2.5		1.09 (0.22,5.53)	1.57 (0.33,7.73)
RISD2.5+VIKD45		1.62 (0.17,17.66)	2.37 (0.25,23.80)
RISD5		0.85 (0.23,3.28)	0.87 (0.23,3.08)
IBAD2.5		0.77 (0.19,3.20)	0.78 (0.19,2.94)
IBAM1		0.72 (0.17,3.19)	0.74 (0.17,3.15)
ZOLY5		0.44 (0.12,1.76)	0.45 (0.11,1.62)
MIND1		0.29 (0.05,1.64)	0.30 (0.05,1.47)
CLOD800		1.02 (0.26,4.37)	1.00 (0.24,3.96)
NERM25		0.36 (0.02,5.33)	0.42 (0.01,4.81)
TILM350		1.77 (0.47,7.15)	1.80 (0.45,6.55)
TILM1400		1.61 (0.42,6.59)	1.64 (0.42,5.98)
ETID200	ALED10+RALD60	2.00 (0.24,40.90)	1.51 (0.17,28.82)
ETID400		2.86 (0.41,58.19)	3.09 (0.40,44.12)
ETID400+HRT		0.85 (0.03,23.55)	0.67 (0.03,18.11)
ETID400+PHOD2		1.63 (0.16,38.64)	1.56 (0.14,36.56)
RISD2.5		4.28 (0.50,98.78)	6.86 (0.76,103.90)
RISD2.5+VIKD45		6.86 (0.43,210.00)	10.30 (0.63,273.20)
RISD5		3.35 (0.51,65.54)	3.71 (0.49,60.50)
IBAD2.5		3.07 (0.43,60.45)	3.33 (0.43,57.25)
IBAM1		2.88 (0.39,58.06)	3.18 (0.39,50.52)
ZOLY5		1.75 (0.27,33.34)	1.89 (0.25,30.67)
MIND1		1.16 (0.13,25.87)	1.26 (0.12,21.72)
CLOD800		4.09 (0.58,81.25)	4.29 (0.52,69.86)
NERM25		1.44 (0.06,66.41)	1.84 (0.05,56.08)
TILM350		7.11 (1.04,139.80)	7.70 (1.03,118.00)
TILM1400		6.48 (0.95,130.00)	7.00 (0.93,111.40)
ETID400	ETID200	1.47 (0.50,4.28)	2.01 (0.64,6.17)
ETID400+HRT		0.42 (0.02,3.06)	0.43 (0.03,3.70)
ETID400+PHOD2		0.81 (0.16,3.69)	1.07 (0.19,4.83)
RISD2.5		2.18 (0.66,6.74)	4.42 (1.22,17.16)
RISD2.5+VIKD45		3.24 (0.45,27.75)	6.65 (0.86,51.70)
RISD5		1.71 (0.70,4.28)	2.40 (0.95,6.59)
IBAD2.5		1.56 (0.57,4.42)	2.17 (0.77,6.35)
IBAM1		1.47 (0.49,4.44)	2.03 (0.67,6.77)
ZOLY5		0.89 (0.36,2.41)	1.23 (0.48,3.45)
MIND1		0.59 (0.13,2.48)	0.83 (0.16,3.53)
CLOD800		2.07 (0.72,6.24)	2.78 (0.97,8.89)
NERM25		0.74 (0.04,9.95)	1.18 (0.04,11.99)
TILM350		3.59 (1.36,9.65)	4.95 (1.88,14.15)
TILM1400		3.30 (1.24,8.86)	4.55 (1.69,13.01)
ETID400+HRT	ETID400	0.28 (0.02,1.84)	0.22 (0.02,1.53)
ETID400+PHOD2		0.56 (0.13,2.00)	0.54 (0.10,2.01)
RISD2.5		1.49 (0.43,4.71)	2.22 (0.64,6.76)
RISD2.5+VIKD45		2.24 (0.29,17.60)	3.27 (0.46,23.52)
RISD5		1.17 (0.55,2.51)	1.21 (0.56,2.60)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
IBAD2.5		1.07 (0.43,2.66)	1.09 (0.44,2.62)
IBAM1		1.00 (0.36,2.71)	1.02 (0.38,2.70)
ZOLY5		0.60 (0.28,1.43)	0.61 (0.28,1.43)
MIND1		0.40 (0.09,1.52)	0.41 (0.09,1.49)
CLOD800		1.41 (0.56,3.78)	1.39 (0.55,3.66)
NERM25		0.50 (0.03,5.94)	0.60 (0.02,5.14)
TILM350		2.43 (1.06,5.79)	2.49 (1.07,5.75)
TILM1400		2.23 (0.95,5.30)	2.28 (0.98,5.28)
ETID400+PHOD2	ETID400+HRT	1.96 (0.20,39.99)	2.51 (0.19,46.49)
RISD2.5		5.24 (0.61,92.40)	10.16 (1.11,152.70)
RISD2.5+VIKD45		7.94 (0.52,205.00)	15.72 (0.95,397.50)
RISD5		4.05 (0.61,64.52)	5.66 (0.77,77.19)
IBAD2.5		3.68 (0.53,62.55)	5.05 (0.65,72.76)
IBAM1		3.47 (0.47,58.84)	4.81 (0.59,68.81)
ZOLY5		2.11 (0.32,35.71)	2.93 (0.39,40.26)
MIND1		1.44 (0.14,28.50)	1.93 (0.18,33.02)
CLOD800		4.95 (0.70,88.65)	6.65 (0.83,95.70)
NERM25		1.79 (0.06,62.29)	2.78 (0.07,83.72)
TILM350		8.54 (1.26,138.80)	11.74 (1.54,163.90)
TILM1400		7.79 (1.15,129.40)	10.77 (1.40,149.50)
RISD2.5	ETID400+PHOD2	2.68 (0.51,14.67)	4.09 (0.86,27.25)
RISD2.5+VIKD45		4.03 (0.39,45.76)	6.26 (0.66,75.87)
RISD5		2.08 (0.56,9.70)	2.25 (0.61,11.44)
IBAD2.5		1.91 (0.46,9.28)	2.03 (0.52,10.83)
IBAM1		1.77 (0.42,9.61)	1.92 (0.45,10.81)
ZOLY5		1.08 (0.30,5.20)	1.15 (0.32,6.10)
MIND1		0.71 (0.12,4.83)	0.76 (0.12,5.95)
CLOD800		2.54 (0.61,13.02)	2.60 (0.66,14.55)
NERM25		0.92 (0.05,14.76)	1.11 (0.04,15.72)
TILM350		4.30 (1.15,21.32)	4.61 (1.23,24.72)
TILM1400		3.95 (1.05,19.46)	4.21 (1.11,23.26)
RISD2.5+VIKD45	RISD2.5	1.51 (0.26,8.85)	1.47 (0.30,7.87)
RISD5		0.78 (0.31,2.29)	0.54 (0.22,1.52)
IBAD2.5		0.71 (0.24,2.48)	0.49 (0.17,1.53)
IBAM1		0.67 (0.22,2.34)	0.46 (0.15,1.48)
ZOLY5		0.41 (0.15,1.37)	0.28 (0.10,0.84)
MIND1		0.27 (0.05,1.35)	0.19 (0.04,0.84)
CLOD800		0.94 (0.31,3.49)	0.62 (0.21,2.22)
NERM25		0.33 (0.02,4.97)	0.28 (0.01,2.69)
TILM350		1.64 (0.58,5.33)	1.13 (0.40,3.51)
TILM1400		1.50 (0.53,4.91)	1.02 (0.36,3.22)
RISD5	RISD2.5+VIKD45	0.53 (0.07,3.56)	0.36 (0.06,2.34)
IBAD2.5		0.48 (0.06,3.58)	0.33 (0.05,2.26)
IBAM1		0.46 (0.05,3.33)	0.31 (0.04,2.21)
ZOLY5		0.28 (0.04,1.96)	0.19 (0.03,1.29)
MIND1		0.18 (0.02,1.84)	0.12 (0.01,1.19)
CLOD800		0.63 (0.08,5.17)	0.42 (0.06,3.19)
NERM25		0.23 (0.01,5.20)	0.18 (0.004,3.43)
TILM350		1.12 (0.13,8.20)	0.76 (0.11,5.14)
TILM1400		1.02 (0.13,7.56)	0.69 (0.10,4.70)
IBAD2.5	RISD5	0.91 (0.45,1.88)	0.90 (0.45,1.80)
IBAM1		0.85 (0.45,1.61)	0.85 (0.46,1.57)
ZOLY5		0.51 (0.30,1.03)	0.50 (0.30,0.98)
MIND1		0.35 (0.09,1.15)	0.34 (0.09,1.12)
CLOD800		1.20 (0.57,2.73)	1.15 (0.56,2.57)
NERM25		0.44 (0.02,4.74)	0.51 (0.02,4.16)
TILM350		2.09 (1.11,4.09)	2.06 (1.11,3.95)
TILM1400		1.91 (1.02,3.76)	1.88 (1.01,3.62)
IBAM1	IBAD2.5	0.94 (0.35,2.39)	0.94 (0.37,2.37)
ZOLY5		0.57 (0.28,1.29)	0.56 (0.28,1.25)
MIND1		0.38 (0.09,1.36)	0.38 (0.09,1.34)
CLOD800		1.32 (0.54,3.42)	1.28 (0.54,3.27)
NERM25		0.47 (0.02,5.36)	0.57 (0.02,4.71)
TILM350		2.30 (1.02,5.10)	2.29 (1.05,5.09)
TILM1400		2.11 (0.93,4.73)	2.10 (0.96,4.60)
ZOLY5	IBAM1	0.60 (0.27,1.57)	0.59 (0.27,1.48)
MIND1		0.41 (0.09,1.56)	0.40 (0.09,1.53)
CLOD800		1.41 (0.53,4.03)	1.36 (0.53,3.80)
NERM25		0.50 (0.03,5.93)	0.59 (0.02,5.20)
TILM350		2.44 (1.01,6.20)	2.44 (1.02,5.94)
TILM1400		2.24 (0.91,5.63)	2.23 (0.93,5.40)
MIND1	ZOLY5	0.67 (0.15,2.20)	0.67 (0.17,2.20)
CLOD800		2.32 (1.01,5.22)	2.27 (1.02,5.03)
NERM25		0.83 (0.04,9.07)	1.00 (0.04,8.11)
TILM350		4.08 (1.82,7.77)	4.09 (1.93,7.59)
TILM1400		3.74 (1.66,7.04)	3.75 (1.75,6.98)
CLOD800	MIND1	3.49 (0.94,16.07)	3.37 (0.96,15.08)
NERM25		1.28 (0.05,17.85)	1.51 (0.05,18.89)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
TILM350		6.04 (1.69,26.26)	6.02 (1.78,24.59)
TILM1400		5.52 (1.56,24.10)	5.50 (1.64,22.66)
NERM25	CLOD800	0.37 (0.02,4.28)	0.43 (0.02,3.72)
TILM350		1.75 (0.69,3.95)	1.79 (0.73,3.94)
TILM1400		1.60 (0.64,3.61)	1.65 (0.67,3.68)
TILM350	NERM25	4.80 (0.43,89.10)	4.05 (0.49,114.80)
TILM1400		4.37 (0.39,84.51)	3.74 (0.45,103.80)
TILM1400	TILM350	0.91 (0.53,1.57)	0.91 (0.55,1.53)

NON-VERTEBRAL FRACTURES

Within the loop formed by placebo, etidronate 400 mg/day, and etidronate 400 mg/day with phosphate 2 g/day, direct evidence from a three-arm trial was found to be inconsistent with evidence from 5 other studies. Since the inconsistent study is the only trial that includes the combination treatment etidronate with phosphate, inconsistency can only be investigated among the comparison of etidronate 400 mg/day to placebo. All six studies comparing etidronate 400 mg/day to placebo and are described in Table 8.5. All studies are published between 1990 to 1998, 4 of 6 are secondary, treatment ranges from 2 to 4 years and age from 53 to 73 years. Four of 6 trials reported all participants had at least one vertebral fracture at baseline. Etidronate 400 mg/day shows greater efficacy compared to placebo except in the inconsistent study. It is possible that Watts et al. (2002) showed an inconsistent result because of unevenly distributed effect modifiers such as race. Watts et al. (2002) included Asian and Caucasian women whereas other studies enrolled Caucasian women only. Two studies were based in Copenhagen and Greece and did not report the race of participants. Another source of inconsistency is variation among intermittent treatment regimen of etidronate. Watts et al. has a 91-day regimen (approximately 3 months): on days 1-3, participants receive daily phosphate 2 g or placebo; on days 4-17, participants receive daily etidronate 400 mg or placebo; on days 18-91, participants receive daily calcium 500 mg. The cycle is repeated 8 times for a total of 2 years. Other studies start with etidronate 400 mg/day for 14 days followed by calcium and/or vitamin D supplementation. Thus, Watts et al. have 3 days less of calcium supplementation, or a total of 24 days over 2 years. This may also contribute to lower efficacy found in etidronate 400 mg/day compared to other studies. In a sensitivity analysis where the inconsistent study was excluded, no significant changes were found from the main analysis. Results are provided in Table 8.6.

Figure 8.3: Network diagram for non-vertebral fractures (main analysis)

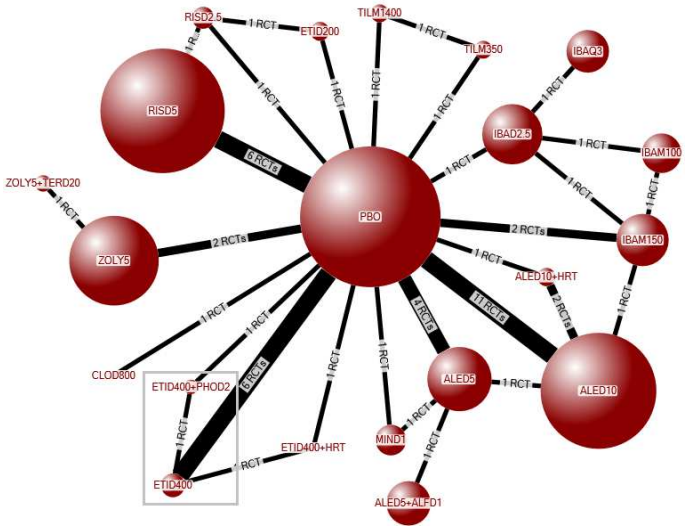


Table 8.5: Studies in the loop formed by placebo, etidronate, and etidronate plus phosphate.

Study	Type	Interventions	Raw fracture data		Treatment duration	Age (yr), mean (SD)	LS T-score	Baseline vertebral fracture	Population
Watts 1990	Secondary	**Placebo** ETI 400 mg/d ETI+PHO	16/104 20/105 14/107	15% 19% 13%	2 years	65.1 (0.6)	-	100%	White and Asian women with osteoporosis, postmenopausal ≥1 yr, healthy, ≥1 but < 4 vertebral compression fractures.
Lyritis 1997	Secondary	Placebo **ETI 400 mg/d**	5/50 3/50	10% 6%	4 years	72.0 (0.4)	-	100%	Age 67 to 77 yrs, postmenopausal, at least 1 vertebral fracture, low BMD below 2 SD, normal biochemical markers.
Meunier 1997	Primary	Placebo **ETI 400 mg/d**	3/27 2/27	11% 7%	2 years	52.7 (0.5)	-	-	Caucasian, ambulatory, active, weighing 45 to 90 kg, within 15% of their normal BMI, Postmeno-pausal 6 to 60 months, normal BMD (within 2 SD of the exp-ected value for their age group).
Pouilles 1997	Primary	Placebo **ETI 400 mg/d**	6/55 3/54	11% 6%	2 years	53.8 (3.1)	-	-	Caucasian, age 45 to 60 yrs, ambulatory, active, between 45 and 80 kg, within 20% of the normal BMI, postmenopausal 6 to 60 mo. prior to enrolment, not been treated with hormones.
Storm 1990	Secondary	Placebo **ETI 400 mg/d**	6/33 5/33	18% 15%	3 years	68.4 (0.9)	-	100%	At least 1 but <4 atraumatic vertebral crush fractures.
Wimalawansa 1998	Secondary	Placebo ETI 400 mg/d	1/18 1/17	6% 6%	4 years	64.9 (0.9)	-	100%	Postmenopausal Caucasian women with ≥ 1 but <4 vertebral fractures, spine BMD at least 2 SD below peak bone mass.

*ETI=etidronate. Bolded studies indicate lower fracture rate within the same comparison.

Table 8.6: Results of the sensitivity analysis for non-vertebral fracture excluding inconsistent study (Watts et al., 1990)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
ALED5	PBO	0.86 (0.54,1.37)	0.86 (0.53,1.38)
ALED5+ALFD1		0.57 (0.20,1.49)	0.56 (0.20,1.53)
ALED10		0.78 (0.60,0.98)	0.78 (0.60,0.97)
ALED10+HRT		0.45 (0.14,1.39)	0.48 (0.14,1.40)
ETID200		0.27 (0.05,1.11)	0.28 (0.05,1.21)
ETID400		0.86 (0.49,1.50)	0.61 (0.29,1.27)
ETID400+HRT		0.62 (0.04,6.33)	0.50 (0.02,7.40)
ETID400+PHOD2		0.66 (0.29,1.48)	N/A
RISD2.5		0.46 (0.12,1.49)	0.49 (0.13,1.54)
RISD5		0.83 (0.58,1.11)	0.84 (0.59,1.10)
IBAD2.5		1.06 (0.63,1.74)	1.07 (0.64,1.74)
IBAM100		1.00 (0.46,2.14)	1.01 (0.47,2.17)
IBAM150		0.98 (0.53,1.83)	1.00 (0.53,1.84)
IBAQ3		0.68 (0.27,1.62)	0.67 (0.28,1.60)
ZOLY5		0.70 (0.43,1.13)	0.70 (0.43,1.11)
ZOLY5+TERD20		0.38 (0.08,1.53)	0.37 (0.08,1.43)
MIND1		0.61 (0.25,1.46)	0.61 (0.25,1.48)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
CLOD800		0.62 (0.02,8.16)	0.67 (0.03,6.69)
TILM350		0.71 (0.29,1.65)	0.71 (0.30,1.67)
TILM1400		0.48 (0.19,1.19)	0.49 (0.19,1.19)
ALED5+ALFD1	ALED5	0.66 (0.26,1.57)	0.65 (0.26,1.58)
ALED10		0.90 (0.53,1.50)	0.90 (0.54,1.53)
ALED10+HRT		0.52 (0.15,1.80)	0.56 (0.15,1.77)
ETID200		0.32 (0.06,1.38)	0.32 (0.06,1.50)
ETID400		0.99 (0.47,2.04)	0.70 (0.29,1.69)
ETID400+HRT		0.72 (0.04,7.78)	0.57 (0.02,9.08)
ETID400+PHOD2		0.77 (0.30,1.92)	N/A
RISD2.5		0.53 (0.13,1.88)	0.56 (0.14,1.95)
RISD5		0.96 (0.54,1.66)	0.97 (0.55,1.65)
IBAD2.5		1.23 (0.61,2.42)	1.24 (0.63,2.46)
IBAM100		1.17 (0.47,2.84)	1.17 (0.48,2.87)
IBAM150		1.14 (0.53,2.45)	1.16 (0.54,2.50)
IBAQ3		0.79 (0.28,2.08)	0.78 (0.28,2.11)
ZOLY5		0.81 (0.41,1.59)	0.82 (0.42,1.58)
ZOLY5+TERD20		0.44 (0.09,1.90)	0.44 (0.09,1.79)
MIND1		0.71 (0.28,1.81)	0.72 (0.27,1.84)
CLOD800		0.72 (0.02,9.51)	0.77 (0.04,8.07)
TILM350		0.82 (0.30,2.14)	0.82 (0.31,2.17)
TILM1400		0.56 (0.20,1.52)	0.56 (0.20,1.56)
ALED10	ALED5+ALFD1	1.37 (0.50,3.98)	1.40 (0.49,3.97)
ALED10+HRT		0.79 (0.18,3.80)	0.86 (0.17,3.81)
ETID200		0.48 (0.07,2.84)	0.50 (0.08,3.00)
ETID400		1.51 (0.49,4.87)	1.09 (0.31,3.97)
ETID400+HRT		1.09 (0.06,14.06)	0.88 (0.03,16.95)
ETID400+PHOD2		1.17 (0.33,4.34)	N/A
RISD2.5		0.79 (0.15,4.13)	0.86 (0.17,4.06)
RISD5		1.46 (0.50,4.24)	1.49 (0.51,4.27)
IBAD2.5		1.87 (0.62,5.92)	1.92 (0.62,6.04)
IBAM100		1.75 (0.51,6.39)	1.81 (0.52,6.49)
IBAM150		1.73 (0.55,5.87)	1.80 (0.55,5.87)
IBAQ3		1.20 (0.31,4.56)	1.20 (0.31,4.74)
ZOLY5		1.24 (0.42,3.88)	1.26 (0.42,3.92)
ZOLY5+TERD20		0.66 (0.11,3.90)	0.68 (0.11,3.59)
MIND1		1.08 (0.31,4.01)	1.11 (0.30,4.10)
CLOD800		1.10 (0.03,17.00)	1.18 (0.05,14.80)
TILM350		1.25 (0.33,4.70)	1.27 (0.34,4.79)
TILM1400		0.85 (0.22,3.30)	0.87 (0.22,3.40)
ALED10+HRT	ALED10	0.58 (0.18,1.78)	0.61 (0.18,1.80)
ETID200		0.35 (0.07,1.50)	0.36 (0.07,1.56)
ETID400		1.10 (0.60,2.01)	0.78 (0.36,1.71)
ETID400+HRT		0.81 (0.05,8.24)	0.64 (0.02,9.67)
ETID400+PHOD2		0.85 (0.36,1.98)	N/A
RISD2.5		0.59 (0.15,2.00)	0.63 (0.17,2.04)
RISD5		1.07 (0.71,1.53)	1.07 (0.72,1.52)
IBAD2.5		1.36 (0.79,2.35)	1.37 (0.81,2.35)
IBAM100		1.28 (0.59,2.82)	1.29 (0.60,2.85)
IBAM150		1.26 (0.68,2.38)	1.28 (0.69,2.38)
IBAQ3		0.87 (0.35,2.15)	0.86 (0.35,2.09)
ZOLY5		0.90 (0.53,1.59)	0.90 (0.53,1.54)
ZOLY5+TERD20		0.48 (0.10,2.04)	0.48 (0.11,1.89)
MIND1		0.79 (0.32,1.96)	0.79 (0.31,1.95)
CLOD800		0.80 (0.03,10.75)	0.85 (0.04,8.69)
TILM350		0.91 (0.36,2.22)	0.91 (0.37,2.20)
TILM1400		0.62 (0.24,1.60)	0.62 (0.24,1.59)
ETID200	ALED10+HRT	0.61 (0.08,3.70)	0.59 (0.08,4.11)
ETID400		1.89 (0.55,6.65)	1.27 (0.34,5.43)
ETID400+HRT		1.37 (0.07,19.15)	1.08 (0.03,19.20)
ETID400+PHOD2		1.47 (0.37,5.91)	N/A
RISD2.5		1.01 (0.17,5.34)	1.01 (0.18,5.59)
RISD5		1.84 (0.57,6.00)	1.75 (0.56,6.25)
IBAD2.5		2.36 (0.69,8.15)	2.23 (0.70,8.39)
IBAM100		2.21 (0.58,8.89)	2.12 (0.58,9.10)
IBAM150		2.17 (0.62,8.21)	2.10 (0.61,8.22)
IBAQ3		1.51 (0.35,6.27)	1.41 (0.35,6.26)
ZOLY5		1.57 (0.46,5.33)	1.46 (0.45,5.54)
ZOLY5+TERD20		0.84 (0.12,4.95)	0.79 (0.12,5.09)
MIND1		1.36 (0.33,5.45)	1.29 (0.32,5.77)
CLOD800		1.37 (0.04,22.36)	1.38 (0.07,22.01)
TILM350		1.56 (0.38,6.37)	1.49 (0.36,6.55)
TILM1400		1.07 (0.25,4.54)	1.03 (0.24,4.63)
ETID400	ETID200	3.12 (0.69,17.36)	2.18 (0.41,13.53)
ETID400+HRT		2.28 (0.10,38.77)	1.82 (0.04,45.19)
ETID400+PHOD2		2.43 (0.47,15.04)	N/A
RISD2.5		1.65 (0.51,6.10)	1.71 (0.52,6.40)
RISD5		3.03 (0.71,16.17)	2.97 (0.69,15.59)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
IBAD2.5		3.87 (0.87,21.61)	3.81 (0.83,21.94)
IBAM100		3.69 (0.73,21.53)	3.60 (0.69,22.97)
IBAM150		3.61 (0.77,19.73)	3.56 (0.73,21.10)
IBAQ3		2.48 (0.46,15.64)	2.42 (0.44,15.86)
ZOLY5		2.59 (0.57,14.34)	2.52 (0.54,14.09)
ZOLY5+TERD20		1.37 (0.17,12.48)	1.34 (0.17,11.91)
MIND1		2.25 (0.41,14.33)	2.19 (0.41,14.12)
CLOD800		2.17 (0.06,52.21)	2.33 (0.08,43.46)
TILM350		2.58 (0.48,16.33)	2.55 (0.46,16.48)
TILM1400		1.75 (0.32,11.54)	1.75 (0.30,11.68)
ETID400+HRT	ETID400	0.74 (0.05,7.15)	0.82 (0.03,12.55)
ETID400+PHOD2		0.78 (0.34,1.77)	N/A
RISD2.5		0.54 (0.13,1.96)	0.78 (0.17,3.21)
RISD5		0.97 (0.51,1.83)	1.36 (0.60,3.07)
IBAD2.5		1.23 (0.60,2.65)	1.76 (0.73,4.34)
IBAM100		1.18 (0.46,3.04)	1.66 (0.57,4.79)
IBAM150		1.15 (0.50,2.67)	1.64 (0.63,4.29)
IBAQ3		0.79 (0.28,2.33)	1.11 (0.35,3.55)
ZOLY5		0.82 (0.39,1.73)	1.15 (0.47,2.81)
ZOLY5+TERD20		0.44 (0.09,2.01)	0.62 (0.12,2.85)
MIND1		0.71 (0.25,2.07)	1.01 (0.32,3.21)
CLOD800		0.73 (0.02,10.27)	1.10 (0.05,11.85)
TILM350		0.82 (0.29,2.38)	1.17 (0.38,3.65)
TILM1400		0.57 (0.19,1.65)	0.79 (0.24,2.64)
ETID400+PHOD2	ETID400+HRT	1.03 (0.09,20.78)	N/A
RISD2.5		0.72 (0.05,15.53)	0.95 (0.05,34.79)
RISD5		1.32 (0.13,23.86)	1.67 (0.11,45.29)
IBAD2.5		1.68 (0.16,29.85)	2.16 (0.14,58.01)
IBAM100		1.60 (0.14,29.42)	2.03 (0.12,60.82)
IBAM150		1.56 (0.14,27.34)	2.03 (0.13,55.40)
IBAQ3		1.06 (0.09,20.58)	1.35 (0.08,39.06)
ZOLY5		1.12 (0.11,20.36)	1.42 (0.09,38.74)
ZOLY5+TERD20		0.60 (0.03,14.54)	0.77 (0.03,25.34)
MIND1		0.98 (0.08,18.22)	1.24 (0.07,36.23)
CLOD800		1.02 (0.01,43.13)	1.26 (0.02,79.53)
TILM350		1.11 (0.10,22.91)	1.41 (0.08,45.18)
TILM1400		0.76 (0.06,16.00)	0.97 (0.05,29.44)
RISD2.5	ETID400+PHOD2	0.68 (0.15,2.93)	N/A
RISD5		1.25 (0.52,2.99)	N/A
IBAD2.5		1.60 (0.61,4.18)	N/A
IBAM100		1.52 (0.49,4.52)	N/A
IBAM150		1.49 (0.53,4.11)	N/A
IBAQ3		1.02 (0.30,3.43)	N/A
ZOLY5		1.05 (0.41,2.75)	N/A
ZOLY5+TERD20		0.57 (0.10,2.90)	N/A
MIND1		0.92 (0.28,3.07)	N/A
CLOD800		0.93 (0.03,14.16)	N/A
TILM350		1.05 (0.32,3.64)	N/A
TILM1400		0.72 (0.21,2.53)	N/A
RISD5	RISD2.5	1.80 (0.54,6.84)	1.70 (0.53,6.39)
IBAD2.5		2.32 (0.63,9.64)	2.20 (0.63,9.04)
IBAM100		2.22 (0.53,9.80)	2.08 (0.52,9.90)
IBAM150		2.19 (0.57,9.07)	2.07 (0.55,8.77)
IBAQ3		1.49 (0.33,7.11)	1.39 (0.33,6.73)
ZOLY5		1.55 (0.42,6.32)	1.44 (0.41,5.76)
ZOLY5+TERD20		0.82 (0.12,5.68)	0.78 (0.12,5.31)
MIND1		1.34 (0.31,6.54)	1.28 (0.30,5.96)
CLOD800		1.31 (0.04,25.92)	1.42 (0.05,20.58)
TILM350		1.54 (0.36,7.32)	1.45 (0.34,7.18)
TILM1400		1.06 (0.24,5.36)	1.00 (0.22,5.10)
IBAD2.5	RISD5	1.27 (0.73,2.37)	1.28 (0.73,2.37)
IBAM100		1.20 (0.54,2.79)	1.21 (0.54,2.83)
IBAM150		1.19 (0.61,2.42)	1.20 (0.61,2.42)
IBAQ3		0.81 (0.32,2.11)	0.80 (0.33,2.05)
ZOLY5		0.84 (0.49,1.56)	0.84 (0.50,1.52)
ZOLY5+TERD20		0.45 (0.10,1.94)	0.45 (0.10,1.83)
MIND1		0.74 (0.30,1.90)	0.74 (0.29,1.90)
CLOD800		0.75 (0.03,10.11)	0.81 (0.04,8.34)
TILM350		0.85 (0.34,2.19)	0.85 (0.35,2.13)
TILM1400		0.58 (0.22,1.57)	0.58 (0.22,1.54)
IBAM100	IBAD2.5	0.94 (0.48,1.90)	0.94 (0.48,1.86)
IBAM150		0.93 (0.50,1.73)	0.93 (0.50,1.74)
IBAQ3		0.64 (0.30,1.33)	0.63 (0.30,1.30)
ZOLY5		0.66 (0.33,1.36)	0.66 (0.33,1.30)
ZOLY5+TERD20		0.36 (0.07,1.58)	0.35 (0.07,1.46)
MIND1		0.58 (0.21,1.61)	0.58 (0.20,1.54)
CLOD800		0.58 (0.02,8.04)	0.62 (0.03,6.79)
TILM350		0.67 (0.24,1.80)	0.67 (0.24,1.81)

Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
TILM1400		0.45 (0.16,1.31)	0.45 (0.16,1.29)
IBAM150	IBAM100	0.99 (0.50,1.93)	0.99 (0.50,1.96)
IBAQ3		0.67 (0.24,1.85)	0.67 (0.24,1.79)
ZOLY5		0.70 (0.28,1.76)	0.70 (0.28,1.71)
ZOLY5+TERD20		0.38 (0.07,1.86)	0.37 (0.07,1.74)
MIND1		0.61 (0.19,1.97)	0.61 (0.19,1.96)
CLOD800		0.61 (0.02,9.14)	0.66 (0.03,7.38)
TILM350		0.70 (0.22,2.25)	0.71 (0.22,2.21)
TILM1400		0.48 (0.14,1.59)	0.48 (0.15,1.59)
IBAQ3	IBAM150	0.68 (0.26,1.80)	0.68 (0.26,1.74)
ZOLY5		0.71 (0.32,1.56)	0.71 (0.32,1.52)
ZOLY5+TERD20		0.38 (0.07,1.75)	0.37 (0.08,1.64)
MIND1		0.62 (0.21,1.81)	0.61 (0.21,1.81)
CLOD800		0.63 (0.02,8.86)	0.67 (0.03,7.22)
TILM350		0.71 (0.24,2.11)	0.71 (0.24,2.03)
TILM1400		0.49 (0.16,1.46)	0.49 (0.16,1.47)
ZOLY5	IBAQ3	1.04 (0.38,2.98)	1.05 (0.39,2.81)
ZOLY5+TERD20		0.55 (0.10,3.02)	0.56 (0.10,2.70)
MIND1		0.90 (0.26,3.22)	0.91 (0.26,3.10)
CLOD800		0.90 (0.03,14.51)	0.99 (0.04,12.12)
TILM350		1.04 (0.30,3.72)	1.06 (0.31,3.51)
TILM1400		0.71 (0.20,2.56)	0.72 (0.20,2.59)
ZOLY5+TERD20	ZOLY5	0.54 (0.13,1.98)	0.53 (0.13,1.93)
MIND1		0.87 (0.32,2.35)	0.87 (0.32,2.40)
CLOD800		0.88 (0.03,11.99)	0.95 (0.05,9.93)
TILM350		1.00 (0.37,2.72)	1.01 (0.38,2.73)
TILM1400		0.68 (0.25,1.94)	0.69 (0.25,1.92)
MIND1	ZOLY5+TERD20	1.66 (0.31,9.05)	1.63 (0.32,9.75)
CLOD800		1.64 (0.05,31.72)	1.78 (0.07,27.81)
TILM350		1.88 (0.36,10.54)	1.90 (0.37,10.80)
TILM1400		1.29 (0.24,7.52)	1.30 (0.24,7.64)
CLOD800	MIND1	1.02 (0.03,14.94)	1.08 (0.05,12.93)
TILM350		1.15 (0.33,3.85)	1.15 (0.34,3.97)
TILM1400		0.79 (0.22,2.78)	0.80 (0.21,2.83)
TILM350	CLOD800	1.14 (0.08,36.83)	1.06 (0.09,22.54)
TILM1400		0.78 (0.05,25.36)	0.73 (0.06,15.21)
TILM1400	TILM350	0.69 (0.26,1.80)	0.69 (0.25,1.79)

WRIST FRACTURES

Two outliers were observed that indicated inconsistency in a two-arm study by Greenspan et al. (1998). The closed loop included placebo, alendronate and zoledronic acid. No inconsistency was observed among zoledronic acid trials. Whereas 3 other trials indicated alendronate was superior to placebo, the inconsistent trial showed alendronate as worse than placebo (Table 8.7). A comparison of study characteristics showed Greenspan et al. had the smallest sample size at 121 participants and only 3 fracture events total, while other studies had 1697 to 4432 participants and upwards of 21 to 153 fractures. The wrist fractures that occurred in the smaller study may have been by chance. Another potential reason for the difference in efficacy of alendronate 10 mg/day is patient disease severity. Greenspan et al. may have had a less severe population compared to other trials, since they did not use BMD as a criterion for inclusion to “allow for greater relevance to the general population of older women”. This may explain why there were fewer fractures in the study. Sensitivity analysis excluding this study showed no significant changes from the main analysis (Table 8.8).

Figure 8.4: Network diagram for wrist fractures (main analysis)

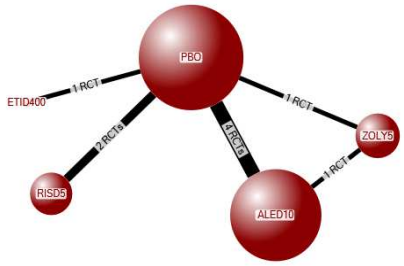


Table 8.7: Studies in the closed loop formed by placebo, alendronate, and zoledronic acid

Study	Type	Interventions	Raw fracture data		Treatment duration	Age (yr), mean (SD)	LS T-score	Baseline vertebral fracture	Population
Greenspan 1998	Secondary	**Placebo** ALE 10 mg/d	0/60 3/60	0% 5%	2.5 years		-	-	Age > 65 yrs, entry criteria were not based on BMD.
Black 1996	Secondary	Placebo **ALE 10 mg/d**	41/1005 22/1022	4% 2%	3 years	70.8 (5.6)	-	100%	Age 55 to 81 yrs, postmenopausal ≥ 2 yrs, BMD more than 2 SD below PBM, at least 1 vertebral deformity.
Cummings 1998	Primary	**Placebo** ALE 10 mg/d	70/2218 83/2214	3% 4%	4 years	67.7 (6.2)	-	0%	Age 55 to 80 yrs, postmenopausal ≥ 2 yrs, FN BMD <0.68g/cm^2 (around 2 SDs below PBM), no vertebral fracture.
Pols 1999	Secondary	Placebo **ALE 10 mg/d**	15/865 6/832	2% 1%	1 year	62.8 (7.4)	-	-	Age < 85 yrs, postmenopausal ≥ 3 yrs, LS BMD at least 2 SDs below mean of premenopausal women, in good health.
Hadji 2012	Secondary	ALE 10 mg/d **ZOL 5 mg/yr**	1/194 0/408	0.5% 0%	1 year	53.9 (8.0)	-2.7 (1.2)	-	Age 55–90 yrs, postmenopausal, with TH or LS T-score ≤ −2.0 and clinical risk factors.
Black 2012	Secondary	Placebo **ZOL 5 mg/yr**	4/616 1/613	0.7% 0.2%	3 years	75.5 (4.9)	-	61%	Women who received 3 ZOL or placebo infusions in the core HORIZON study.

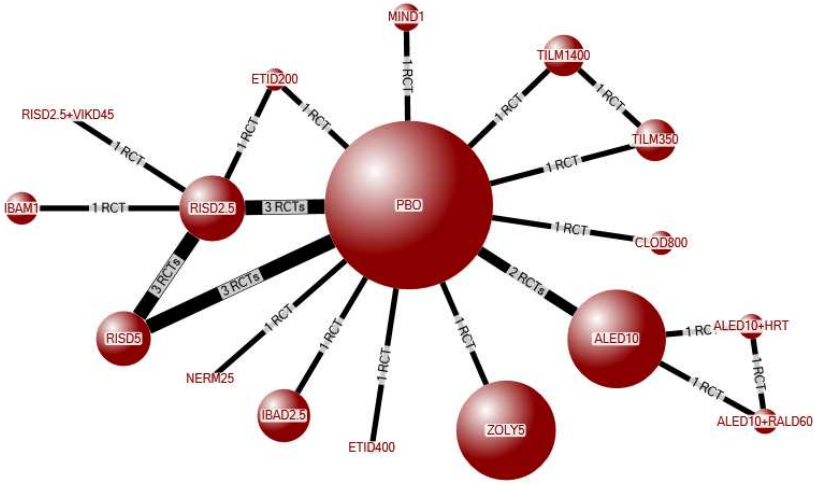
*ALE=alendronate, ZOL=zoledronic acid. Bolded studies indicate lower fracture rate within the same comparison.

Table 8.8: Results of the sensitivity analysis for wrist fracture excluding inconsistent study (Greenspan et al., 1998)

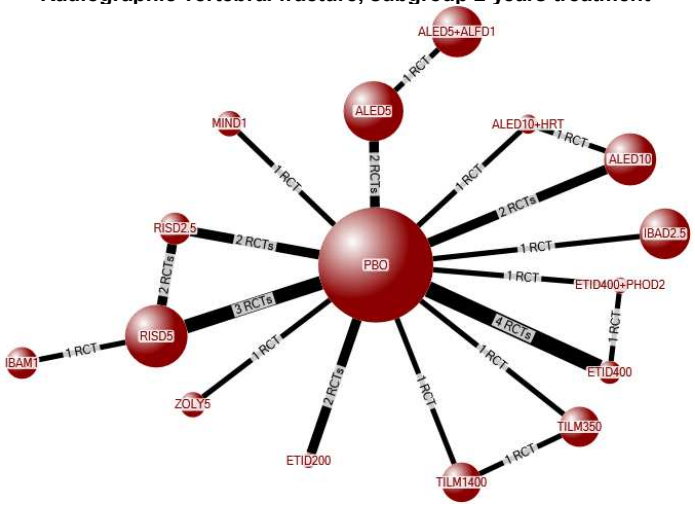
Treatment	Reference	Main analysis OR (95% CrI)	Sensitivity analysis OR (95% CrI)
ALED10	PBO	0.81 (0.44,1.49)	0.75 (0.37,1.28)
ETID400		0.91 (0.09,8.04)	0.90 (0.09,8.65)
RISD5		0.59 (0.20,1.66)	0.59 (0.21,1.65)
ZOLY5		0.19 (0.02,1.04)	0.18 (0.02,1.08)
ETID400	ALED10	1.12 (0.10,10.75)	1.22 (0.11,12.75)
RISD5		0.73 (0.21,2.43)	0.80 (0.25,2.80)
ZOLY5		0.23 (0.02,1.31)	0.25 (0.03,1.50)
RISD5	ETID400	0.66 (0.06,8.18)	0.67 (0.05,8.31)
ZOLY5		0.20 (0.01,3.67)	0.19 (0.01,3.81)
ZOLY5	RISD5	0.31 (0.02,2.46)	0.30 (0.03,2.43)

APPENDIX 9: NETWORK DIAGRAMS FOR SUBGROUP ANALYSES OF TREATMENT DURATIONS

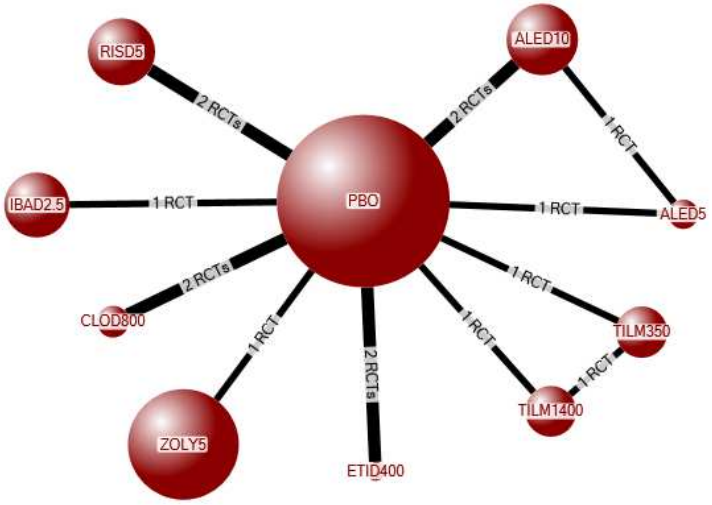
Radiographic vertebral fracture, subgroup 1 year treatment



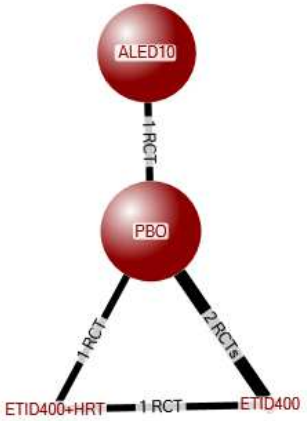
Radiographic vertebral fracture, subgroup 2 years treatment



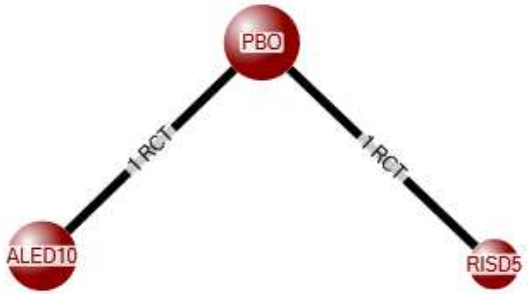
Radiographic vertebral fracture, subgroup 3 years treatment



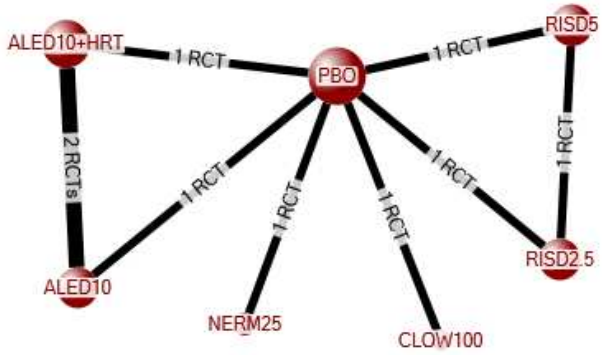
Radiographic vertebral fracture, subgroup 4 years treatment



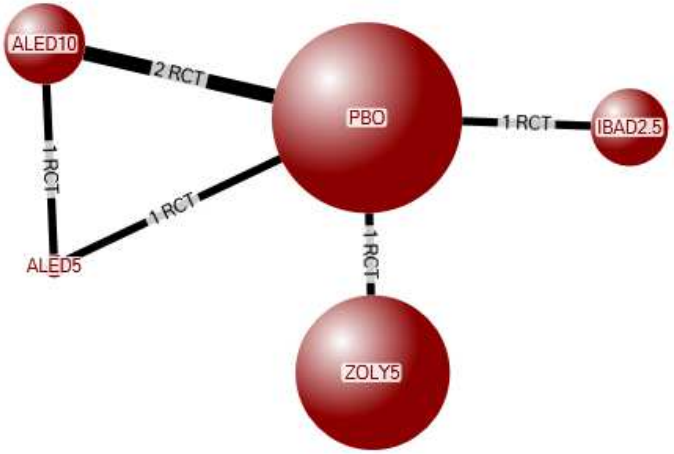
Radiographic vertebral fracture, subgroup 5 years treatment



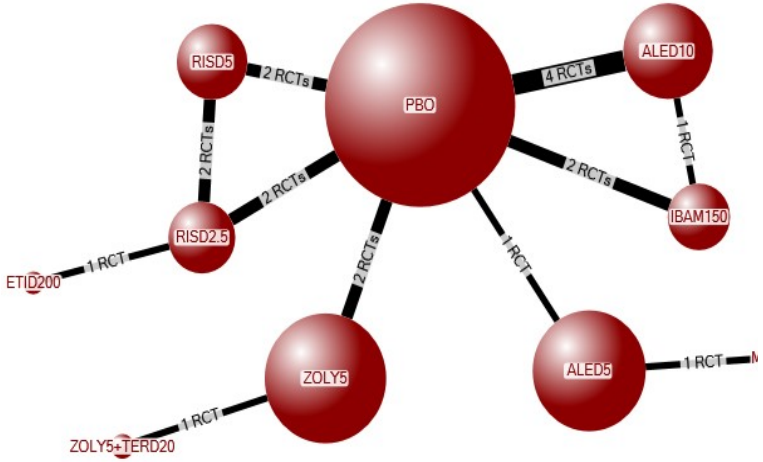
Clinical vertebral fracture, subgroup 2 years treatment



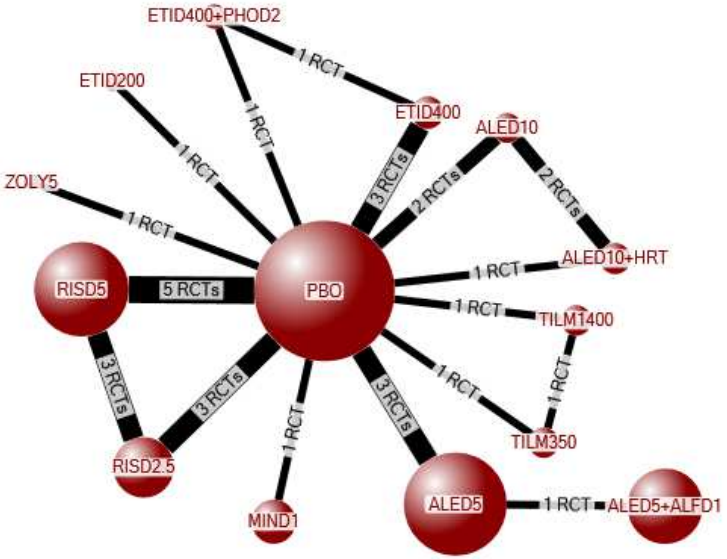
Clinical vertebral fracture, subgroup 3 years treatment



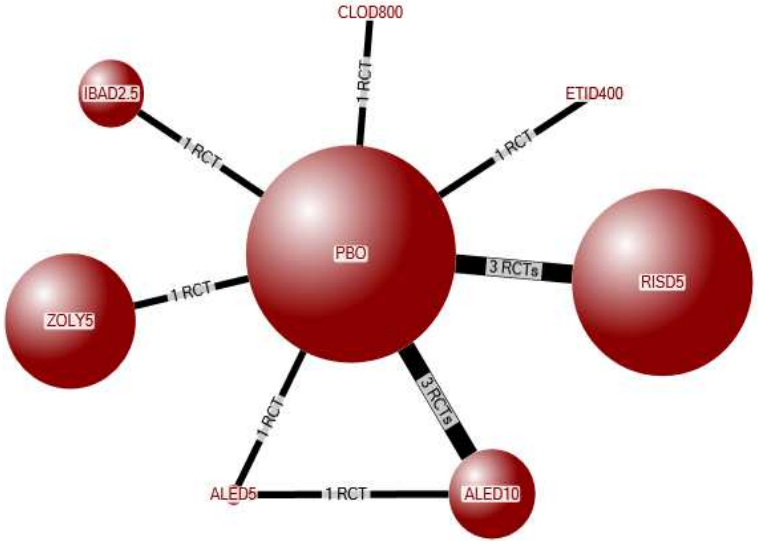
Non-vertebral fracture, subgroup 1 year treatment



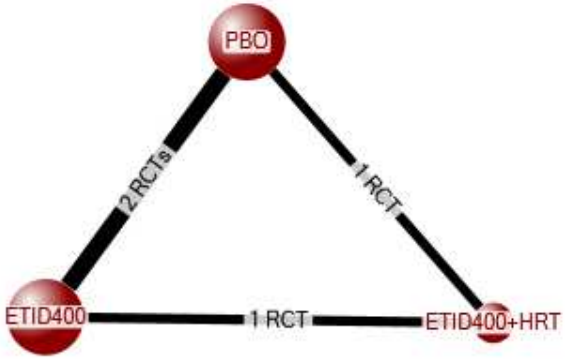
Non-vertebral fracture, subgroup 2 years treatment



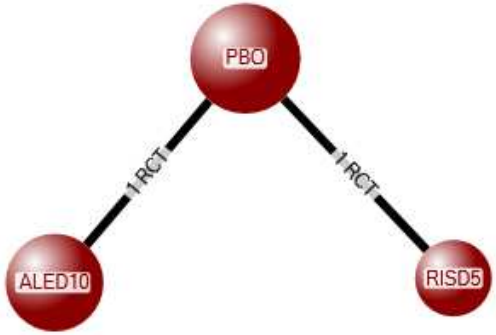
Non-vertebral fracture, subgroup 3 years treatment



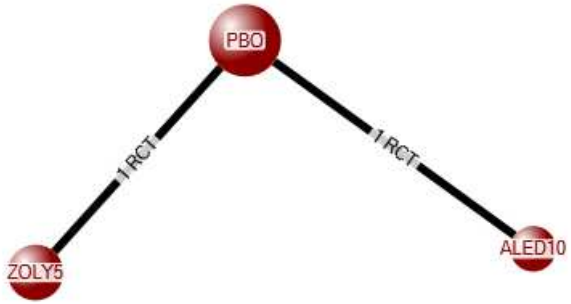
Non-vertebral fracture, subgroup 4 years treatment



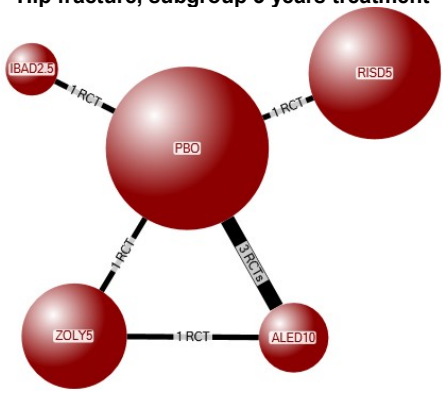
Non-vertebral fracture, subgroup 5 years treatment



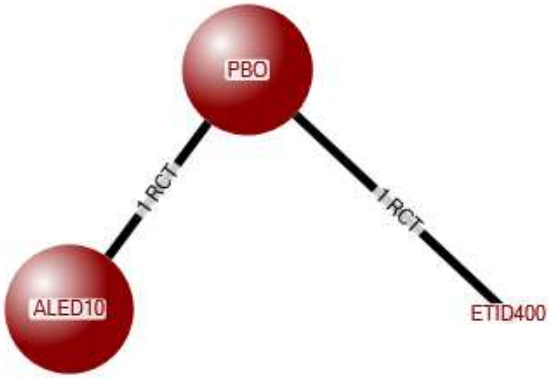
Hip fracture, subgroup 2 years treatment



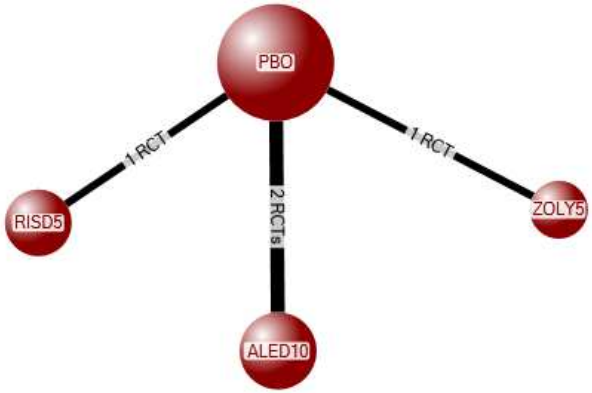
Hip fracture, subgroup 3 years treatment



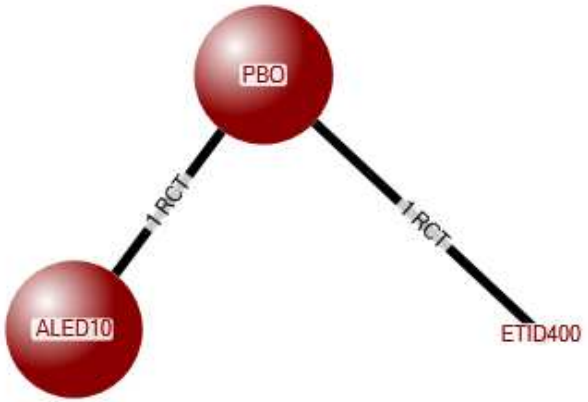
Hip fracture, subgroup 4 years treatment



Wrist fracture, subgroup 3 years treatment



Wrist fracture, subgroup 4 years treatment



APPENDIX 10: SENSITIVITY ANALYSES FOR NETWORK META-ANALYSES

Sensitivity analyses for radiographic vertebral fracture

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ALED5	PBO	0.56 (0.33,0.97)	ALED5	PBO	0.49 (0.17,1.38)	ALED5	PBO	0.54 (0.31,0.91)	ALED5	PBO	0.53 (0.28,0.94)	ALED5	PBO	0.51 (0.23,1.06)
ALED5 +ALFD1		0.50 (0.24,1.04)	ALED10		0.57 (0.40,0.82)	ALED5 +ALFD1		0.49 (0.24,1.01)	ALED5 +ALFD1		0.48 (0.22,1.02)	ALED10		0.51 (0.37,0.70)
ALED10		0.58 (0.45,0.77)	ALED10 +HRT		0.41 (0.07,2.27)	ALED10		0.58 (0.44,0.76)	ALED10		0.51 (0.38,0.70)	ALED10 +HRT		0.39 (0.06,2.18)
ALED10 +HRT		0.60 (0.17,2.44)	ALED10 +RALD60		0.12 (0.01,0.87)	ALED10 +HRT		0.61 (0.17,2.15)	ETID200		0.04 (0.002,0.24)	ALED10 +RALD60		0.11 (0.01,0.92)
ALED10 +RALD60		0.14 (0.01,1.27)	ETID200		0.49 (0.18,1.40)	ALED10 +RALD60		0.15 (0.01,1.17)	RISD5		0.54 (0.38,0.78)	ETID400		0.47 (0.18,1.20)
ETID200		0.27 (0.12,0.62)	ETID400		0.46 (0.17,1.22)	ETID200		0.32 (0.14,0.72)	IBAD2.5		0.48 (0.28,0.83)	ETID400 +HRT		0.12 (0.01,0.85)
ETID400		0.49 (0.26,0.91)	ETID400 +HRT		0.11 (0.01,0.85)	ETID400		0.44 (0.22,0.85)	ZOLY5		0.27 (0.19,0.43)	ETID400 +PHOD2		0.26 (0.06,0.91)
ETID400 +HRT		0.12 (0.01,0.85)	ETID400 +PHOD2		0.26 (0.05,0.96)	ETID400 +HRT		0.10 (0.01,0.83)	MIND1		0.18 (0.05,0.53)	IBAD2.5		0.48 (0.28,0.85)
ETID400 +PHOD2		0.26 (0.05,0.90)	RISD2.5		0.35 (0.04,2.46)	ETID400 +PHOD2		0.24 (0.05,0.84)	CLOD800		0.57 (0.29,1.09)	MIND1		0.19 (0.05,0.58)
RISD2.5		0.43 (0.19,0.93)	RISD5		0.16 (.0005,3.92)	RISD2.5		0.77 (0.32,1.80)	TILM350		1.11 (0.70,1.73)	CLOD800		2.72 (0.26,42.74)
RISD2.5 +VIKD45		0.54 (0.10,3.37)	IBAM1		0.30 (0.03,2.43)	RISD2.5 +VIKD45		1.23 (0.18,8.72)	TILM1400		1.01 (0.64,1.60)	ALED10	ALED5	0.99 (0.46,2.33)

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
RISD5		0.54 (0.38,0.73)	ZOLY5		0.25 (0.13,0.46)	RISD5		0.53 (0.38,0.73)	ALED5 +ALFD1	ALED5	0.91 (0.55,1.50)	ALED10 +HRT		0.76 (0.11,4.99)
IBAD2.5		0.48 (0.28,0.83)	NERM25		0.26 (0.01,2.73)	IBAD2.5		0.48 (0.28,0.83)	ALED10		0.97 (0.51,1.91)	ALED10 +RALD60		0.21 (0.01,2.15)
IBAM1		0.38 (0.13,0.96)	ALED10	ALED5	1.16 (0.41,3.51)	IBAM1		0.66 (0.23,1.77)	ETID200		0.07 (0.003,0.52)	ETID400		0.92 (0.27,3.29)
ZOLY5		0.30 (0.21,0.47)	ALED10 +HRT		0.84 (0.10,6.08)	ZOLY5		0.27 (0.19,0.43)	RISD5		1.03 (0.52,2.13)	ETID400 +HRT		0.24 (0.01,1.87)
MIND1		0.21 (0.06,0.59)	ALED10 +RALD60		0.25 (0.01,2.39)	ALED5 +ALFD1	ALED5	0.92 (0.55,1.51)	IBAD2.5		0.92 (0.41,2.05)	ETID400 +PHOD2		0.50 (0.09,2.41)
CLOD800		0.61 (0.33,1.14)	ETID200		0.99 (0.24,4.70)	ALED10		1.08 (0.60,1.96)	ZOLY5		0.51 (0.26,1.11)	IBAD2.5		0.95 (0.38,2.50)
NERM25		0.26 (0.01,2.55)	ETID400		0.95 (0.22,4.32)	ALED10 +HRT		1.14 (0.28,4.31)	MIND1		0.34 (0.09,1.20)	MIND1		0.37 (0.08,1.42)
TILM350		1.11 (0.70,1.75)	ETID400 +HRT		0.22 (0.01,2.36)	ALED10 +RALD60		0.27 (0.02,2.43)	CLOD800		1.08 (0.44,2.66)	CLOD800		5.37 (0.46,87.36)
TILM1400		1.01 (0.64,1.62)	ETID400 +PHOD2		0.52 (0.08,2.83)	ETID200		0.59 (0.22,1.55)	TILM350		2.10 (1.02,4.52)	ALED10+HRT	ALED10	0.76 (0.13,4.07)
ALED5 +ALFD1	ALED5	0.88 (0.53,1.46)	RISD2.5		0.72 (0.06,6.75)	ETID400		0.82 (0.35,1.93)	TILM1400		1.92 (0.92,4.17)	ALED10 +RALD60		0.21 (0.01,1.73)
ALED10		1.04 (0.57,1.84)	RISD5		0.33 (0.001,9.08)	ETID400 +HRT		0.19 (0.01,1.72)	ALED10	ALED5 +ALFD1	1.07 (0.48,2.44)	ETID400		0.92 (0.33,2.42)
ALED10 +HRT		1.04 (0.28,4.66)	IBAM1		0.61 (0.05,6.61)	ETID400 +PHOD2		0.44 (0.09,1.72)	ETID200		0.08 (0.003,0.61)	ETID400 +HRT		0.24 (0.01,1.73)
ALED10 +RALD60		0.25 (0.01,2.31)	ZOLY5		0.50 (0.15,1.75)	RISD2.5		1.43 (0.53,3.98)	RISD5		1.14 (0.49,2.71)	ETID400 +PHOD2		0.51 (0.10,1.83)
ETID200		0.49 (0.19,1.31)	NERM25		0.54 (0.02,6.55)	RISD2.5 +VIKD45		2.25 (0.31,17.11)	IBAD2.5		1.01 (0.39,2.61)	IBAD2.5		0.95 (0.50,1.77)
ETID400		0.88 (0.38,1.89)	ALED10 +HRT	ALED10	0.72 (0.12,3.87)	RISD5		0.99 (0.52,1.87)	ZOLY5		0.56 (0.25,1.40)	MIND1		0.37 (0.09,1.18)
ETID400 +HRT		0.22 (0.01,1.58)	ALED10 +RALD60		0.21 (0.01,1.47)	IBAD2.5		0.89 (0.42,1.94)	MIND1		0.37 (0.09,1.44)	CLOD800		5.26 (0.49,86.40)
ETID400 +PHOD2		0.47 (0.09,1.81)	ETID200		0.85 (0.31,2.62)	IBAM1		1.22 (0.38,3.88)	CLOD800		1.20 (0.42,3.28)	ALED10 +RALD60	ALED10 +HRT	0.26 (0.01,2.26)
RISD2.5		0.77 (0.29,1.94)	ETID400		0.81 (0.28,2.30)	ZOLY5		0.50 (0.27,1.03)	TILM350		2.32 (0.96,5.72)	ETID400		1.20 (0.15,9.30)
RISD2.5 +VIKD45		0.95 (0.16,6.77)	ETID400 +HRT		0.19 (0.01,1.53)	ALED10	ALED5 +ALFD1	1.18 (0.55,2.54)	TILM1400		2.12 (0.87,5.26)	ETID400 +HRT		0.29 (0.01,5.01)
RISD5		0.95 (0.50,1.73)	ETID400 +PHOD2		0.45 (0.09,1.75)	ALED10 +HRT		1.24 (0.29,5.33)	ETID200	ALED10	0.07 (0.003,0.50)	ETID400 +PHOD2		0.65 (0.07,6.37)
IBAD2.5		0.87 (0.39,1.84)	RISD2.5		0.61 (0.06,4.49)	ALED10 +RALD60		0.30 (0.02,2.80)	RISD5		1.06 (0.66,1.72)	IBAD2.5		1.24 (0.20,8.45)
IBAM1		0.68 (0.21,1.95)	RISD5		0.28 (0.001,7.01)	ETID200		0.65 (0.21,1.91)	IBAD2.5		0.94 (0.50,1.76)	MIND1		0.49 (0.05,3.89)
ZOLY5		0.53 (0.28,1.06)	IBAM1		0.52 (0.05,4.36)	ETID400		0.89 (0.33,2.45)	ZOLY5		0.52 (0.33,0.90)	CLOD800		7.13 (0.36,203.5)
MIND1		0.37 (0.09,1.20)	ZOLY5		0.43 (0.21,0.87)	ETID400 +HRT		0.20 (0.01,2.00)	MIND1		0.35 (0.10,1.10)	ETID400	ALED10 +RALD60	4.47 (0.43,102.3)
CLOD800		1.09 (0.49,2.43)	NERM25		0.45 (0.02,4.85)	ETID400 +PHOD2		0.48 (0.09,2.06)	CLOD800		1.11 (0.53,2.29)	ETID400 +HRT		1.13 (0.04,37.28)
NERM25		0.46 (0.01,4.75)	ALED10 +RALD60	ALED10+HRT	0.29 (0.02,2.70)	RISD2.5		1.56 (0.52,4.79)	TILM350		2.17 (1.25,3.71)	ETID400 +PHOD2		2.53 (0.16,71.52)
TILM350		1.96 (0.97,3.96)	ETID200		1.20 (0.17,9.67)	RISD2.5 +VIKD45		2.46 (0.32,19.83)	TILM1400		1.99 (1.14,3.45)	IBAD2.5		4.60 (0.50,91.76)
TILM1400		1.81 (0.88,3.61)	ETID400		1.15 (0.15,9.43)	RISD5		1.08 (0.48,2.43)	RISD5	ETID200	14.59 (2.16,326.1)	MIND1		1.83 (0.15,48.66)
ALED10	ALED5 +ALFD1	1.18 (0.54,2.53)	ETID400 +HRT		0.26 (0.01,4.52)	IBAD2.5		0.98 (0.39,2.46)	IBAD2.5		13.05 (1.84,307.0)	CLOD800		26.61 (1.07,2154)
ALED10 +HRT		1.19 (0.30,5.87)	ETID400 +PHOD2		0.63 (0.06,5.70)	IBAM1		1.34 (0.37,4.63)	ZOLY5		7.33 (1.09,166.0)	ETID400 +HRT	ETID400	0.27 (0.02,1.97)

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ALED10 +RALD60		0.28 (0.01,2.85)	RISD2.5		0.86 (0.05,12.70)	ZOLY5		0.55 (0.25,1.32)	MIND1		5.00 (0.51,137.6)	ETID400 +PHOD2		0.55 (0.12,2.02)
ETID200		0.56 (0.19,1.65)	RISD5		0.37 (0.001,16.1)	ALED10 +HRT	ALED10	1.05 (0.30,3.61)	CLOD800		15.53 (2.11,365.1)	IBAD2.5		1.04 (0.35,3.07)
ETID400		0.99 (0.38,2.46)	IBAM1		0.72 (0.04,11.95)	ALED10 +RALD60		0.26 (0.02,2.00)	TILM350		30.15 (4.23,661.7)	MIND1		0.41 (0.07,1.74)
ETID400 +HRT		0.25 (0.02,1.88)	ZOLY5		0.60 (0.10,3.97)	ETID200		0.55 (0.22,1.30)	TILM1400		27.40 (3.96,606.8)	CLOD800		5.88 (0.47,98.58)
ETID400 +PHOD2		0.54 (0.09,2.23)	NERM25		0.63 (0.02,12.71)	ETID400		0.77 (0.37,1.55)	IBAD2.5	RISD5	0.89 (0.46,1.70)	ETID400 +PHOD2	ETID400 +HRT	2.09 (0.21,49.30)
RISD2.5		0.88 (0.29,2.51)	ETID200	ALED10 +RALD60	4.26 (0.44,91.90)	ETID400 +HRT		0.17 (0.01,1.49)	ZOLY5		0.49 (0.30,0.89)	IBAD2.5		3.94 (0.52,67.65)
RISD2.5 +VIKD45		1.08 (0.17,8.32)	ETID400		3.95 (0.40,84.83)	ETID400 +PHOD2		0.41 (0.09,1.50)	MIND1		0.33 (0.09,1.05)	MIND1		1.59 (0.14,32.16)
RISD5		1.08 (0.47,2.36)	ETID400 +HRT		0.94 (0.04,29.36)	RISD2.5		1.34 (0.53,3.25)	CLOD800		1.05 (0.49,2.17)	CLOD800		24.81 (1.16,843.3)
IBAD2.5		0.98 (0.39,2.43)	ETID400 +PHOD2		2.13 (0.17,49.43)	RISD2.5 +VIKD45		2.15 (0.30,15.43)	TILM350		2.04 (1.14,3.59)	IBAD2.5	ETID400 +PHOD2	1.86 (0.48,9.58)
IBAM1		0.77 (0.22,2.50)	RISD2.5		3.16 (0.16,93.77)	RISD5		0.92 (0.59,1.39)	TILM1400		1.87 (1.03,3.31)	MIND1		0.74 (0.11,4.82)
ZOLY5		0.60 (0.27,1.42)	RISD5		1.35 (0.004,73.4)	IBAD2.5		0.83 (0.45,1.52)	ZOLY5	IBAD2.5	0.56 (0.29,1.15)	CLOD800		10.74 (0.73,248.2)
MIND1		0.41 (0.09,1.52)	IBAM1		2.69 (0.12,84.06)	IBAM1		1.14 (0.38,3.18)	MIND1		0.38 (0.10,1.27)	MIND1	IBAD2.5	0.39 (0.09,1.34)
CLOD800		1.24 (0.49,3.21)	ZOLY5		2.07 (0.26,41.55)	ZOLY5		0.47 (0.30,0.81)	CLOD800		1.18 (0.50,2.77)	CLOD800		5.63 (0.51,91.88)
NERM25		0.53 (0.01,5.65)	NERM25		2.12 (0.06,83.77)	ALED10 +RALD60	ALED10 +HRT	0.25 (0.02,1.70)	TILM350		2.30 (1.13,4.61)	CLOD800	MIND1	14.57(0.90,28 8.4)
TILM350		2.23 (0.93,5.26)	ETID400	ETID200	0.95 (0.22,3.78)	ETID200		0.52 (0.11,2.42)	TILM1400		2.11 (1.04,4.24)			
TILM1400		2.06 (0.85,4.90)	ETID400 +HRT		0.22 (0.01,2.10)	ETID400		0.73 (0.18,2.97)	MIND1	ZOLY5	0.67 (0.18,2.13)			
ALED10 +HRT	ALED10	1.03 (0.30,4.12)	ETID400 +PHOD2		0.52 (0.07,2.77)	ETID400 +HRT		0.15 (0.01,1.80)	CLOD800		2.12 (0.93,4.40)			
ALED10 +RALD60		0.24 (0.01,2.12)	RISD2.5		0.71 (0.08,4.93)	ETID400 +PHOD2		0.39 (0.05,2.42)	TILM350		4.13 (2.10,7.24)			
ETID200		0.47 (0.20,1.10)	RISD5		0.33 (0.001,8.22)	RISD2.5		1.27 (0.27,5.54)	TILM1400		3.78 (1.92,6.63)			
ETID400		0.84 (0.42,1.65)	IBAM1		0.61 (0.06,4.80)	RISD2.5 +VIKD45		2.07 (0.20,18.81)	CLOD800	MIND1	3.18 (0.86,12.43)			
ETID400 +HRT		0.21 (0.01,1.45)	ZOLY5		0.51 (0.15,1.56)	RISD5		0.87 (0.24,3.24)	TILM350		6.18 (1.90,23.33)			
ETID400 +PHOD2		0.45 (0.09,1.58)	NERM25		0.52 (0.02,6.46)	IBAD2.5		0.80 (0.20,3.12)	TILM1400		5.62 (1.72,21.15)			
RISD2.5		0.74 (0.30,1.67)	ETID400 +HRT	ETID400	0.24 (0.02,1.90)	IBAM1		1.09 (0.22,5.29)	TILM350	CLOD800	1.94 (0.87,4.47)			
RISD2.5 +VIKD45		0.92 (0.16,5.88)	ETID400 +PHOD2		0.55 (0.11,2.26)	ZOLY5		0.45 (0.12,1.73)	TILM1400		1.78 (0.79,4.08)			
RISD5		0.92 (0.59,1.36)	RISD2.5		0.76 (0.07,6.61)	ETID200	ALED10 +RALD60	2.12 (0.24,35.38)	TILM1400	TILM350	0.92 (0.58,1.46)			
IBAD2.5		0.83 (0.45,1.50)	RISD5		0.34 (0.001,11.2)	ETID400		2.95 (0.35,51.42)						
IBAM1		0.65 (0.22,1.70)	IBAM1		0.65 (0.06,6.48)	ETID400 +HRT		0.67 (0.02,17.17)						
ZOLY5		0.51 (0.33,0.87)	ZOLY5		0.53 (0.17,1.71)	ETID400 +PHOD2		1.64 (0.11,37.52)						
MIND1		0.36 (0.09,1.04)	NERM25		0.56 (0.03,7.10)	RISD2.5		5.22 (0.57,102.80)						
CLOD800		1.05 (0.54,2.08)	ETID400 +PHOD2	ETID400 +HRT	2.30 (0.18,40.45)	RISD2.5 +VIKD45		8.31 (0.51,251.40)						

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
NERM25		0.44 (0.01,4.37)	RISD2.5		3.16 (0.16,83.83)	RISD5		3.59 (0.44,60.74)						
TILM350		1.90 (1.11,3.20)	RISD5		1.36 (0.01,91.55)	IBAD2.5		3.26 (0.39,55.06)						
TILM1400		1.73 (1.01,2.95)	IBAM1		2.74 (0.12,76.16)	IBAM1		4.44 (0.44,94.97)						
ALED10 +RALD60	ALED10 +HRT	0.25 (0.01,1.69)	ZOLY5		2.25 (0.27,29.99)	ZOLY5		1.84 (0.22,30.48)						
ETID200		0.45 (0.10,2.13)	NERM25		2.29 (0.08,69.58)	ETID400	ETID200	1.39 (0.51,3.81)						
ETID400		0.83 (0.17,3.12)	RISD2.5	ETID400 +PHOD2	1.45 (0.10,14.69)	ETID400 +HRT		0.31 (0.01,3.10)						
ETID400 +HRT		0.20 (0.01,1.84)	RISD5		0.62 (0.002,24.97)	ETID400 +PHOD2		0.75 (0.14,3.34)						
ETID400 +PHOD2		0.45 (0.05,2.40)	IBAM1		1.23 (0.08,14.53)	RISD2.5		2.42 (0.83,7.63)						
RISD2.5		0.71 (0.14,3.23)	ZOLY5		0.97 (0.22,5.24)	RISD2.5 +VIKD45		3.88 (0.54,30.72)						
RISD2.5 +VIKD45		0.89 (0.10,8.02)	NERM25		1.02 (0.04,16.28)	RISD5		1.68 (0.72,4.01)						
RISD5		0.90 (0.21,3.12)	RISD5	RISD2.5	0.44 (0.001,19.65)	IBAD2.5		1.53 (0.57,4.07)						
IBAD2.5		0.81 (0.17,3.15)	IBAM1		0.85 (0.42,1.76)	IBAM1		2.07 (0.60,7.28)						
IBAM1		0.63 (0.11,3.14)	ZOLY5		0.71 (0.09,7.30)	ZOLY5		0.86 (0.35,2.15)						
ZOLY5		0.51 (0.12,1.84)	NERM25		0.75 (0.02,17.59)	ETID400 +HRT	ETID400	0.22 (0.01,1.84)						
MIND1		0.35 (0.05,1.73)	IBAM1	RISD5	1.92 (0.04,830.1)	ETID400 +PHOD2		0.53 (0.12,2.13)						
CLOD800		1.03 (0.22,4.08)	ZOLY5		1.51 (0.06,536.8)	RISD2.5		1.77 (0.55,5.03)						
NERM25		0.42 (0.01,5.91)	NERM25		1.78 (0.02,418.2)	RISD2.5 +VIKD45		2.83 (0.37,21.94)						
TILM350		1.87 (0.42,6.68)	ZOLY5	IBAM1	0.82 (0.09,8.96)	RISD5		1.21 (0.58,2.56)						
TILM1400		1.70 (0.38,6.10)	NERM25		0.87 (0.02,22.20)	IBAD2.5		1.09 (0.46,2.61)						
ETID200	ALED10 +RALD60	1.98 (0.20,36.21)	NERM25	ZOLY5	1.05 (0.05,11.73)	IBAM1		1.50 (0.42,4.83)						
ETID400		3.62 (0.32,63.24)				ZOLY5		0.61 (0.29,1.39)						
ETID400 +HRT		0.96 (0.03,20.58)				ETID400 +PHOD2	ETID400 +HRT	2.49 (0.19,58.71)						
ETID400 +PHOD2		1.92 (0.11,52.75)				RISD2.5		7.89 (0.70,172.1)						
RISD2.5		3.06 (0.30,58.55)				RISD2.5 +VIKD45		13.28 (0.53,507.1)						
RISD2.5 +VIKD45		3.87 (0.24,99.75)				RISD5		5.44 (0.61,99.77)						
RISD5		3.75 (0.41,69.36)				IBAD2.5		4.94 (0.53,91.49)						
IBAD2.5		3.47 (0.35,63.2)				IBAM1		6.82 (0.53,161.5)						
IBAM1		2.68 (0.24,53.8)				ZOLY5		2.83 (0.31,49.83)						
ZOLY5		2.15 (0.23,37.8)				RISD2.5	ETID400 +PHOD2	3.33 (0.66,17.58)						
MIND1		1.47 (0.10,29.9)				RISD2.5 +VIKD45		5.19 (0.48,64.74)						

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
CLOD800		4.34 (0.44,78.5)				RISD5		2.25 (0.59,10.04)						
NERM25		1.88 (0.03,78.9)				IBAD2.5		2.05 (0.50,9.51)						
TILM350		7.91 (0.86,143)				IBAM1		2.85 (0.51,16.05)						
TILM1400		7.21 (0.77,125)				ZOLY5		1.15 (0.31,5.34)						
ETID400	ETID200	1.77 (0.64,4.94)				RISD2.5 +VIKD45	RISD2.5	1.60 (0.29,9.40)						
ETID400 +HRT		0.45 (0.03,3.60)				RISD5		0.68 (0.29,1.67)						
ETID400 +PHOD2		0.96 (0.16,4.36)				IBAD2.5		0.62 (0.23,1.75)						
RISD2.5		1.56 (0.53,4.56)				IBAM1		0.85 (0.47,1.51)						
RISD2.5 +VIKD45		1.96 (0.31,14.41)				ZOLY5		0.35 (0.14,0.95)						
RISD5		1.94 (0.81,4.61)				RISD5	RISD2.5 +VIKD45	0.43 (0.06,2.95)						
IBAD2.5		1.76 (0.65,4.68)				IBAD2.5		0.39 (0.05,2.91)						
IBAM1		1.37 (0.39,4.58)				IBAM1		0.53 (0.08,3.19)						
ZOLY5		1.09 (0.44,2.75)				ZOLY5		0.22 (0.03,1.62)						
MIND1		0.75 (0.16,2.83)				IBAD2.5	RISD5	0.90 (0.49,1.72)						
CLOD800		2.22 (0.81,6.23)				IBAM1		1.25 (0.43,3.42)						
NERM25		0.93 (0.02,10.44)				ZOLY5		0.50 (0.32,0.93)						
TILM350		4.03 (1.57,10.15)				IBAM1	IBAD2.5	1.37 (0.41,4.14)						
TILM1400		3.68 (1.45,9.18)				ZOLY5		0.56 (0.29,1.15)						
ETID400 +HRT	ETID400	0.25 (0.02,1.80)				ZOLY5	IBAM1	0.41 (0.14,1.32)						
ETID400 +PHOD2		0.54 (0.11,1.99)												
RISD2.5		0.89 (0.31,2.40)												
RISD2.5 +VIKD45		1.10 (0.18,7.70)												
RISD5		1.10 (0.54,2.20)												
IBAD2.5		0.99 (0.43,2.29)												
IBAM1		0.77 (0.24,2.35)												
ZOLY5		0.61 (0.30,1.32)												
MIND1		0.42 (0.11,1.41)												
CLOD800		1.25 (0.52,3.07)												
NERM25		0.53 (0.01,6.00)												
TILM350		2.27 (1.05,4.85)												

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
TILM1400		2.07 (0.96,4.49)												
ETID400 +PHOD2	ETID400 +HRT	2.19 (0.17,37.32)												
RISD2.5		3.53 (0.46,49.85)												
RISD2.5 +VIKD45		4.49 (0.34,89.41)												
RISD5		4.30 (0.62,63.91)												
IBAD2.5		3.91 (0.52,59.55)												
IBAM1		3.06 (0.38,45.60)												
ZOLY5		2.44 (0.35,38.11)												
MIND1		1.66 (0.16,29.11)												
CLOD800		4.94 (0.68,84.42)												
NERM25		2.14 (0.03,56.13)												
TILM350		8.95 (1.25,143.4)												
TILM1400		8.22 (1.14,134.2)												
RISD2.5	ETID400 +PHOD2	1.66 (0.37,9.08)												
RISD2.5 +VIKD45		2.10 (0.27,23.68)												
RISD5		2.03 (0.59,10.20)												
IBAD2.5		1.84 (0.48,9.79)												
IBAM1		1.44 (0.30,8.58)												
ZOLY5		1.14 (0.31,5.92)												
MIND1		0.77 (0.14,5.44)												
CLOD800		2.31 (0.59,12.54)												
NERM25		0.98 (0.02,13.75)												
TILM350		4.20 (1.15,22.45)												
TILM1400		3.83 (1.03,20.60)												
RISD2.5 +VIKD45	RISD2.5	1.25 (0.27,6.73)												
RISD5		1.24 (0.56,2.88)												
IBAD2.5		1.13 (0.44,3.07)												
IBAM1		0.88 (0.49,1.55)												
ZOLY5		0.70 (0.29,1.85)												
MIND1		0.47 (0.11,1.78)												

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
CLOD800		1.43 (0.52,4.08)												
NERM25		0.60 (0.02,7.24)												
TILM350		2.57 (1.04,6.82)												
TILM1400		2.35 (0.96,6.23)												
RISD5	RISD2.5 +VIKD45	1.00 (0.16,5.59)												
IBAD2.5		0.90 (0.14,5.25)												
IBAM1		0.70 (0.12,3.59)												
ZOLY5		0.56 (0.09,3.24)												
MIND1		0.38 (0.04,2.98)												
CLOD800		1.14 (0.16,7.02)												
NERM25		0.48 (0.01,7.40)												
TILM350		2.06 (0.31,12.33)												
TILM1400		1.88 (0.28,11.23)												
IBAD2.5	RISD5	0.90 (0.48,1.74)												
IBAM1		0.71 (0.25,1.87)												
ZOLY5		0.55 (0.34,1.02)												
MIND1		0.38 (0.10,1.18)												
CLOD800		1.14 (0.58,2.37)												
NERM25		0.49 (0.01,4.83)												
TILM350		2.06 (1.19,3.74)												
TILM1400		1.89 (1.09,3.44)												
IBAM1	IBAD2.5	0.78 (0.24,2.32)												
ZOLY5		0.62 (0.33,1.28)												
MIND1		0.43 (0.10,1.40)												
CLOD800		1.27 (0.56,2.93)												
NERM25		0.53 (0.01,5.22)												
TILM350		2.28 (1.13,4.73)												
TILM1400		2.08 (1.03,4.33)												
ZOLY5	IBAM1	0.79 (0.29,2.53)												

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
MIND1		0.54 (0.11,2.28)												
CLOD800		1.60 (0.53,5.46)												
NERM25		0.68 (0.02,8.88)												
TILM350		2.91 (1.03,9.21)												
TILM1400		2.67 (0.95,8.51)												
MIND1	ZOLY5	0.68 (0.18,2.10)												
CLOD800		2.04 (0.97,4.16)												
NERM25		0.86 (0.02,8.69)												
TILM350		3.72 (1.89,6.57)												
TILM1400		3.41 (1.73,6.03)												
CLOD800	MIND1	2.99 (0.87,12.39)												
NERM25		1.26 (0.03,17.83)												
TILM350		5.38 (1.69,21.69)												
TILM1400		4.94 (1.56,19.26)												
NERM25	CLOD800	0.42 (0.01,4.32)												
TILM350		1.82 (0.84,3.79)												
TILM1400		1.65 (0.76,3.55)												
TILM350	NERM25	4.28 (0.42,161.7)												
TILM1400		3.92 (0.39,148.9)												
TILM1400	TILM350	0.92 (0.57,1.46)												

TRT=treatment of interest, REF=reference treatment, PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, RALD60=raloxifene 60 mg/day, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, HRT=hormone replacement therapy, RISD2.5=risedronate 2.5 mg/day, VIKD45=vitamin K 45 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM1=ibandronate 1 mg/month, ZOLY5=zoledronic acid 5 mg/year, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, NERM25=neridronate 25 mg/month, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Sensitivity analyses for clinical vertebral fracture

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**
ALED5	PBO	0.97 (0.07,10.69)	ALED10	PBO	0.44 (0.25,0.77)	ALED5	PBO	0.97 (0.06,10.49)	ALED10	PBO	0.43 (0.16,1.20)	ALED5	PBO	0.94 (0.04,10.02)
ALED10		0.44 (0.26,0.72)	IBAM150		0.40 (0.09,1.85)	ALED10		0.44 (0.26,0.72)	IBAD2.5		0.52 (0.19,1.48)	ALED10		0.41 (0.17,0.95)
ALED10 +HRT		0.98 (0.19,5.24)	ZOLY5		0.22 (0.10,0.48)	ALED10+HRT		1.00 (0.19,5.75)	ZOLY5		0.22 (0.08,0.62)	ALED10 +HRT		0.94 (0.05,50.10)
RISD2.5		1.05 (0.39,3.06)	IBAM150	ALED10	0.91 (0.24,3.81)	RISD2.5		1.06 (0.40,2.98)	IBAD2.5	ALED10	1.19 (0.28,5.06)	IBAD2.5		0.52 (0.20,1.31)
RISD5		0.93 (0.32,2.78)	ZOLY5		0.51 (0.19,1.34)	RISD5		0.94 (0.34,2.57)	ZOLY5		0.51 (0.12,2.20)	ALED10	ALED5	0.44 (0.04,10.20)
IBAD2.5		0.52 (0.24,1.08)	ZOLY5	IBAM150	0.55 (0.10,2.90)	IBAD2.5		0.52 (0.25,1.06)	ZOLY5	IBAD2.5	0.43 (0.10,1.79)	ALED10 +HRT		1.03 (0.02,104.80)
IBAM150		0.42 (0.10,1.66)				IBAM150		0.40 (0.09,1.72)				IBAD2.5		0.55 (0.04,12.84)
ZOLY5		0.22 (0.10,0.44)				ZOLY5		0.22 (0.11,0.44)				ALED10 +HRT	ALED10	2.28 (0.13,110.10)
CLOW100		0.80 (0.03,19.55)				ALED10	ALED5	0.44 (0.04,8.28)				IBAD2.5		1.24 (0.37,4.57)
NERM25		0.41 (0.03,4.08)				ALED10+HRT		1.04 (0.06,26.86)				IBAD2.5	ALED10 +HRT	0.54 (0.01,12.28)
ALED10	ALED5	0.44 (0.04,6.29)				RISD2.5		1.09 (0.09,23.85)						
ALED10 +HRT		1.01 (0.05,18.19)				RISD5		0.96 (0.08,19.10)						
RISD2.5		1.07 (0.08,19.12)				IBAD2.5		0.53 (0.05,10.00)						
RISD5		0.95 (0.08,17.27)				IBAM150		0.41 (0.03,10.26)						
IBAD2.5		0.53 (0.04,8.21)				ZOLY5		0.22 (0.02,4.43)						
IBAM150		0.42 (0.02,7.75)				ALED10+HRT	ALED10	2.23 (0.44,13.12)						
ZOLY5		0.23 (0.02,3.50)				RISD2.5		2.39 (0.79,7.79)						
CLOW100		0.76 (0.02,48.38)				RISD5		2.12 (0.69,6.59)						
NERM25		0.42 (0.01,14.99)				IBAD2.5		1.19 (0.48,2.81)						
ALED10 +HRT	ALED10	2.21 (0.44,11.72)				IBAM150		0.93 (0.21,3.46)						
RISD2.5		2.38 (0.81,7.98)				ZOLY5		0.50 (0.21,1.18)						
RISD5		2.12 (0.66,7.58)				RISD2.5	ALED10 +HRT	1.05 (0.14,7.44)						
IBAD2.5		1.18 (0.48,2.93)				RISD5		0.94 (0.12,6.47)						
IBAM150		0.95 (0.25,3.54)				IBAD2.5		0.51 (0.08,3.11)						
ZOLY5		0.50 (0.20,1.20)				IBAM150		0.42 (0.04,2.99)						
CLOW100		1.81 (0.07,43.9)				ZOLY5		0.22 (0.03,1.35)						
NERM25		0.94 (0.06,9.88)				RISD5	RISD2.5	0.89 (0.32,2.48)						
RISD2.5	ALED10 +HRT	1.07 (0.15,7.05)				IBAD2.5		0.49 (0.14,1.69)						

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
RISD5		0.96 (0.12,6.74)				IBAM150		0.38 (0.06,2.21)						
IBAD2.5		0.53 (0.08,3.03)				ZOLY5		0.21 (0.06,0.70)						
IBAM150		0.43 (0.05,3.45)				IBAD2.5	RISD5	0.55 (0.16,1.92)						
ZOLY5		0.22 (0.04,1.30)				IBAM150		0.43 (0.07,2.48)						
CLOW100		0.78 (0.02,24.26)				ZOLY5		0.23 (0.07,0.79)						
NERM25		0.43 (0.01,6.87)				IBAM150	IBAD2.5	0.77 (0.14,4.08)						
RISD5	RISD2.5	0.89 (0.31,2.47)				ZOLY5		0.42 (0.15,1.17)						
IBAD2.5		0.49 (0.13,1.73)				ZOLY5	IBAM150	0.54 (0.11,2.92)						
IBAM150		0.39 (0.07,2.18)												
ZOLY5		0.21 (0.06,0.71)												
CLOW100		0.76 (0.02,21.1)												
NERM25		0.39 (0.02,4.58)												
IBAD2.5	RISD5	0.55 (0.15,2.10)												
IBAM150		0.45 (0.07,2.68)												
ZOLY5		0.23 (0.06,0.86)												
CLOW100		0.87 (0.02,23.18)												
NERM25		0.43 (0.02,5.49)												
IBAM150	IBAD2.5	0.81 (0.17,3.92)												
ZOLY5		0.42 (0.15,1.18)												
CLOW100		1.53 (0.05,38.6)												
NERM25		0.79 (0.05,8.94)												
ZOLY5	IBAM150	0.52 (0.11,2.55)												
CLOW100		1.94 (0.05,53.6)												
NERM25		0.98 (0.05,14.67)												
CLOW100	ZOLY5	3.69 (0.13,96.0)												
NERM25		1.85 (0.11,21.8)												
NERM25	CLOW100	0.50 (0.01,28.9)												

TRT=treatment of interest, REF=reference treatment, PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM150=ibandronate 150 mg/month, ZOLY5=zoledronic acid 5 mg/year, CLOW100=clodronate 100 mg/week, NERM25=neridronate 25 mg/month.

Sensitivity analyses for non-vertebral fracture (randomized denominator, low risk of bias, five major bisphosphonates, primary outcome, bisphosphonate naïve)

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ALED5	PBO	0.87 (0.53,1.38)	ALED5	PBO	1.59 (0.76,3.43)	ALED5	PBO	0.82 (0.49,1.33)	ALED5	PBO	0.57 (0.18,1.62)	ALED5	PBO	0.99 (0.60,1.58)
ALED5 +ALFD1		0.54 (0.19,1.46)	ALED10		0.81 (0.63,0.96)	ALED5 +ALFD1		0.54 (0.18,1.49)	ALED5 +ALFD1		0.37 (0.08,1.55)	ALED10		0.82 (0.64,1.05)
ALED10		0.78 (0.60,0.97)	ETID200		0.30 (0.02,2.42)	ALED10		0.78 (0.60,0.97)	ALED10		0.82 (0.56,1.19)	ALED10 +HRT		0.23 (.001,3.61)
ALED10 +HRT		0.46 (0.14,1.34)	ETID400		0.96 (0.50,1.78)	ALED10 +HRT		0.46 (0.13,1.41)	RISD5		0.88 (0.56,1.23)	ETID400		1.06 (0.56,1.94)
ETID200		0.27 (0.05,1.04)	ETID400 +HRT		0.69 (0.04,9.23)	ETID200		0.28 (0.06,1.10)	IBAD2.5		1.12 (0.58,2.18)	ETID400 +HRT		0.69 (0.04,8.16)
ETID400		0.83 (0.47,1.49)	ETID400 +PHOD2		0.71 (0.30,1.55)	ETID400		0.84 (0.48,1.47)	ZOLY5		0.73 (0.39,1.35)	ETID400 +PHOD2		0.73 (0.33,1.60)
ETID400 +HRT		0.71 (0.04,7.98)	RISD2.5		0.56 (0.04,6.99)	ETID400 +HRT		0.72 (0.04,8.57)	MIND1		0.71 (0.24,2.00)	IBAD2.5		1.11 (0.70,1.74)
ETID400 +PHOD2		0.65 (0.28,1.49)	IBAD2.5		0.85 (0.27,2.27)	ETID400 +PHOD2		0.66 (0.29,1.49)	ALED5 +ALFD1	ALED5	0.65 (0.25,1.71)	IBAM100		1.09 (0.51,2.51)
RISD2.5		0.47 (0.13,1.46)	IBAM100		0.86 (0.30,2.23)	RISD2.5		0.47 (0.13,1.60)	ALED10		1.43 (0.47,4.79)	IBAM150		1.12 (0.50,2.66)
RISD5		0.83 (0.58,1.09)	IBAM150		0.91 (0.40,1.90)	RISD5		0.83 (0.58,1.10)	RISD5		1.53 (0.49,5.02)	ZOLY5		0.24 (0.02,2.07)
IBAD2.5		1.06 (0.63,1.74)	ZOLY5		0.72 (0.48,1.01)	IBAD2.5		1.06 (0.63,1.75)	IBAD2.5		1.96 (0.56,7.33)	MIND1		0.64 (0.28,1.46)
IBAM100		1.01 (0.46,2.12)	ZOLY5 +TERD20		0.36 (0.08,1.29)	IBAM100		1.01 (0.46,2.14)	ZOLY5		1.28 (0.39,4.64)	CLOD800		0.60 (0.04,6.71)
IBAM150		1.00 (0.54,1.83)	MIND1		0.73 (0.07,4.35)	IBAM150		1.00 (0.53,1.82)	MIND1		1.23 (0.27,5.87)	ALED10	ALED5	0.83 (0.49,1.44)
IBAQ3		0.66 (0.27,1.62)	ALED10	ALED5	0.50 (0.23,1.07)	IBAQ3		0.68 (0.27,1.69)	ALED10	ALED5 +ALFD1	2.24 (0.50,10.15)	ALED10 +HRT		0.23 (.001,3.86)
ZOLY5		0.70 (0.42,1.13)	ETID200		0.18 (0.01,1.72)	ZOLY5		0.70 (0.42,1.13)	RISD5		2.37 (0.52,10.68)	ETID400		1.07 (0.47,2.39)
ZOLY5 +TERD20		0.37 (0.08,1.52)	ETID400		0.60 (0.22,1.57)	ZOLY5 +TERD20		0.37 (0.08,1.54)	IBAD2.5		3.05 (0.62,15.50)	ETID400 +HRT		0.69 (0.04,9.03)
MIND1		0.65 (0.26,1.56)	ETID400 +HRT		0.44 (0.02,6.02)	ALED5 +ALFD1	ALED5	0.65 (0.26,1.60)	ZOLY5		2.00 (0.42,9.77)	ETID400 +PHOD2		0.74 (0.30,1.90)
CLOD800		0.42 (0.03,4.54)	ETID400 +PHOD2		0.44 (0.14,1.31)	ALED10		0.94 (0.55,1.63)	MIND1		1.91 (0.31,11.65)	IBAD2.5		1.12 (0.58,2.24)
TILM350		0.70 (0.29,1.65)	RISD2.5		0.36 (0.02,5.45)	ALED10 +HRT		0.56 (0.15,1.90)	RISD5	ALED10	1.08 (0.59,1.77)	IBAM100		1.12 (0.46,2.90)
TILM1400		0.47 (0.18,1.18)	IBAD2.5		0.53 (0.14,1.90)	ETID200		0.34 (0.07,1.44)	IBAD2.5		1.37 (0.64,2.93)	IBAM150		1.14 (0.45,3.08)
ALED5 +ALFD1	ALED5	0.63 (0.25,1.52)	IBAM100		0.53 (0.15,1.79)	ETID400		1.03 (0.49,2.19)	ZOLY5		0.89 (0.43,1.84)	ZOLY5		0.25 (0.02,2.26)
ALED10		0.89 (0.53,1.52)	IBAM150		0.56 (0.19,1.62)	ETID400 +HRT		0.88 (0.04,11.23)	MIND1		0.86 (0.28,2.61)	MIND1		0.65 (0.27,1.60)
ALED10 +HRT		0.53 (0.15,1.71)	ZOLY5		0.45 (0.19,1.00)	ETID400 +PHOD2		0.80 (0.31,2.12)	IBAD2.5	RISD5	1.27 (0.62,2.91)	CLOD800		0.60 (0.03,7.27)
ETID200		0.31 (0.06,1.32)	ZOLY5 +TERD20		0.23 (0.04,0.94)	RISD2.5		0.58 (0.14,2.12)	ZOLY5		0.82 (0.43,1.83)	ALED10 +HRT	ALED10	0.27 (0.001,4.30)
ETID400		0.96 (0.46,2.06)	MIND1		0.46 (0.05,2.30)	RISD5		1.00 (0.55,1.80)	MIND1		0.81 (0.27,2.53)	ETID400		1.28 (0.64,2.49)
ETID400 +HRT		0.82 (0.04,9.37)	ETID200	ALED10	0.37 (0.03,2.97)	IBAD2.5		1.28 (0.64,2.64)	ZOLY5	IBAD2.5	0.65 (0.26,1.64)	ETID400 +HRT		0.83 (0.05,10.21)
ETID400 +PHOD2		0.75 (0.28,1.96)	ETID400		1.20 (0.61,2.29)	IBAM100		1.23 (0.49,3.02)	MIND1		0.63 (0.18,2.15)	ETID400 +PHOD2		0.88 (0.39,2.05)
RISD2.5		0.54 (0.13,1.85)	ETID400 +HRT		0.87 (0.05,11.92)	IBAM150		1.22 (0.55,2.62)	MIND1	ZOLY5	0.97 (0.28,3.21)	IBAD2.5		1.35 (0.80,2.24)

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**
RISD5		0.95 (0.53,1.66)	ETID400 +PHOD2		0.89 (0.37,2.00)	IBAQ3		0.82 (0.30,2.33)				IBAM100		1.33 (0.59,3.11)
IBAD2.5		1.22 (0.61,2.48)	RISD2.5		0.71 (0.05,8.72)	ZOLY5		0.85 (0.43,1.72)				IBAM150		1.37 (0.58,3.24)
IBAM100		1.16 (0.47,2.87)	IBAD2.5		1.06 (0.33,2.86)	ZOLY5 +TERD20		0.45 (0.09,1.98)				ZOLY5		0.30 (0.02,2.60)
IBAM150		1.16 (0.54,2.54)	IBAM100		1.07 (0.37,2.83)	ALED10	ALED5 +ALFD1	1.44 (0.51,4.26)				MIND1		0.78 (0.33,1.82)
IBAQ3		0.76 (0.28,2.16)	IBAM150		1.14 (0.51,2.31)	ALED10 +HRT		0.86 (0.17,4.06)				CLOD800		0.72 (0.04,8.27)
ZOLY5		0.81 (0.41,1.61)	ZOLY5		0.89 (0.59,1.37)	ETID200		0.52 (0.08,3.06)				ETID400	ALED10 +HRT	4.79 (0.27,1104)
ZOLY5 +TERD20		0.43 (0.09,1.89)	ZOLY5 +TERD20		0.45 (0.10,1.65)	ETID400		1.57 (0.49,5.30)				ETID400 +HRT		3.15 (0.06,1512)
MIND1		0.75 (0.28,1.93)	MIND1		0.91 (0.08,5.59)	ETID400 +HRT		1.34 (0.06,19.76)				ETID400 +PHOD2		3.28 (0.17,829.8)
CLOD800		0.49 (0.03,5.80)	ETID400	ETID200	3.23 (0.36,42.78)	ETID400 +PHOD2		1.23 (0.33,4.78)				IBAD2.5		4.93 (0.29,1121)
TILM350		0.81 (0.31,2.17)	ETID400 +HRT		2.58 (0.06,75.07)	RISD2.5		0.88 (0.16,4.41)				IBAM100		5.00 (0.26,1190)
TILM1400		0.54 (0.19,1.55)	ETID400 +PHOD2		2.37 (0.25,33.68)	RISD5		1.53 (0.52,4.60)				IBAM150		5.06 (0.28,1201)
ALED10	ALED5 +ALFD1	1.42 (0.51,4.12)	RISD2.5		1.95 (0.53,7.12)	IBAD2.5		1.97 (0.63,6.46)				ZOLY5		1.09 (0.02,237.4)
ALED10 +HRT		0.83 (0.18,3.76)	IBAD2.5		2.81 (0.27,43.84)	IBAM100		1.87 (0.51,6.87)				MIND1		3.03 (0.15,743.3)
ETID200		0.50 (0.08,2.70)	IBAM100		2.91 (0.27,43.04)	IBAM150		1.87 (0.56,6.20)				CLOD800		2.97 (0.04,775.9)
ETID400		1.53 (0.48,5.18)	IBAM150		3.07 (0.32,41.09)	IBAQ3		1.27 (0.32,5.12)				ETID400 +HRT	ETID400	0.63 (0.04,7.90)
ETID400 +HRT		1.31 (0.06,17.13)	ZOLY5		2.40 (0.28,29.05)	ZOLY5		1.30 (0.42,4.20)				ETID400 +PHOD2		0.70 (0.31,1.60)
ETID400 +PHOD2		1.19 (0.32,4.59)	ZOLY5 +TERD20		1.19 (0.10,19.87)	ZOLY5 +TERD20		0.69 (0.11,4.07)				IBAD2.5		1.04 (0.50,2.32)
RISD2.5		0.86 (0.16,3.86)	MIND1		2.57 (0.11,48.72)	ALED10 +HRT	ALED10	0.60 (0.17,1.83)				IBAM100		1.04 (0.40,2.92)
RISD5		1.52 (0.53,4.41)	ETID400 +HRT	ETID400	0.73 (0.04,10.13)	ETID200		0.36 (0.07,1.47)				IBAM150		1.07 (0.40,3.04)
IBAD2.5		1.95 (0.64,6.32)	ETID400 +PHOD2		0.74 (0.33,1.61)	ETID400		1.09 (0.60,2.01)				ZOLY5		0.23 (0.02,2.26)
IBAM100		1.86 (0.51,6.72)	RISD2.5		0.60 (0.04,7.54)	ETID400 +HRT		0.94 (0.05,11.27)				MIND1		0.62 (0.22,1.64)
IBAM150		1.85 (0.56,6.18)	IBAD2.5		0.88 (0.24,2.83)	ETID400 +PHOD2		0.85 (0.36,2.00)				CLOD800		0.57 (0.03,6.87)
IBAQ3		1.23 (0.32,4.83)	IBAM100		0.89 (0.26,2.75)	RISD2.5		0.61 (0.16,2.11)				ETID400 +PHOD2	ETID400+HRT	1.07 (0.08,20.31)
ZOLY5		1.29 (0.42,4.10)	IBAM150		0.94 (0.33,2.50)	RISD5		1.07 (0.71,1.54)				IBAD2.5		1.61 (0.13,31.24)
ZOLY5 +TERD20		0.69 (0.11,3.83)	ZOLY5		0.74 (0.37,1.55)	IBAD2.5		1.36 (0.81,2.38)				IBAM100		1.59 (0.12,35.87)
MIND1		1.19 (0.32,4.53)	ZOLY5 +TERD20		0.37 (0.08,1.63)	IBAM100		1.29 (0.60,2.81)				IBAM150		1.65 (0.11,37.59)
CLOD800		0.77 (0.05,11.15)	MIND1		0.78 (0.06,4.97)	IBAM150		1.29 (0.70,2.38)				ZOLY5		0.37 (0.01,14.57)
TILM350		1.29 (0.35,4.95)	ETID400 +PHOD2	ETID400 +HRT	1.00 (0.07,17.24)	IBAQ3		0.87 (0.35,2.25)				MIND1		0.96 (0.07,21.12)
TILM1400		0.87 (0.22,3.53)	RISD2.5		0.79 (0.02,51.08)	ZOLY5		0.90 (0.53,1.56)				CLOD800		0.82 (0.02,50.19)
ALED10	ALED10	0.59	IBAD2.5		1.17	ZOLY5		0.47				IBAD2.5	ETID400	1.51

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
+HRT		(0.19,1.75)			(0.07,24.71)	+TERD20		(0.10,2.05)					+PHOD2	(0.62,3.74)
ETID200		0.35 (0.07,1.39)	IBAM100		1.20 (0.07,23.92)	ETID200	ALED10 +HRT	0.61 (0.09,3.78)				IBAM100		1.50 (0.51,4.61)
ETID400		1.08 (0.58,2.03)	IBAM150		1.30 (0.08,24.38)	ETID400		1.82 (0.53,7.14)				IBAM150		1.53 (0.52,4.68)
ETID400 +HRT		0.93 (0.05,10.47)	ZOLY5		1.03 (0.07,16.27)	ETID400 +HRT		1.62 (0.07,22.98)				ZOLY5		0.33 (0.03,3.24)
ETID400 +PHOD2		0.84 (0.35,2.01)	ZOLY5 +TERD20		0.48 (0.02,11.20)	ETID400 +PHOD2		1.41 (0.36,6.29)				MIND1		0.89 (0.28,2.73)
RISD2.5		0.61 (0.16,1.92)	MIND1		0.96 (0.04,31.37)	RISD2.5		1.03 (0.18,5.78)				CLOD800		0.80 (0.05,10.36)
RISD5		1.07 (0.71,1.54)	RISD2.5	ETID400 +PHOD2	0.81 (0.05,10.88)	RISD5		1.78 (0.56,6.48)				IBAM100	IBAD2.5	0.99 (0.53,1.97)
IBAD2.5		1.37 (0.80,2.39)	IBAD2.5		1.22 (0.29,4.42)	IBAD2.5		2.30 (0.68,8.85)				IBAM150		1.02 (0.51,2.14)
IBAM100		1.31 (0.59,2.81)	IBAM100		1.23 (0.32,4.11)	IBAM100		2.18 (0.58,9.41)				ZOLY5		0.22 (0.02,2.00)
IBAM150		1.30 (0.70,2.41)	IBAM150		1.27 (0.41,3.81)	IBAM150		2.16 (0.62,8.83)				MIND1		0.58 (0.23,1.50)
IBAQ3		0.86 (0.35,2.17)	ZOLY5		1.01 (0.42,2.51)	IBAQ3		1.48 (0.35,6.92)				CLOD800		0.53 (0.03,6.34)
ZOLY5		0.91 (0.52,1.58)	ZOLY5 +TERD20		0.51 (0.09,2.32)	ZOLY5		1.52 (0.46,5.89)				IBAM150	IBAM100	1.03 (0.54,1.93)
ZOLY5 +TERD20		0.48 (0.11,2.02)	MIND1		1.06 (0.08,7.59)	ZOLY5 +TERD20		0.80 (0.12,5.22)				ZOLY5		0.22 (0.02,2.29)
MIND1		0.84 (0.32,2.11)	IBAD2.5	RISD2.5	1.48 (0.09,25.91)	ETID400	ETID200	3.00 (0.68,16.94)				MIND1		0.58 (0.19,1.80)
CLOD800		0.55 (0.04,6.14)	IBAM100		1.55 (0.09,24.99)	ETID400 +HRT		2.52 (0.09,49.85)				CLOD800		0.54 (0.03,6.74)
TILM350		0.91 (0.37,2.24)	IBAM150		1.59 (0.11,25.42)	ETID400 +PHOD2		2.34 (0.48,13.86)				ZOLY5	IBAM150	0.21 (0.02,2.27)
TILM1400		0.61 (0.23,1.61)	ZOLY5		1.26 (0.10,19.62)	RISD2.5		1.68 (0.54,5.97)				MIND1		0.56 (0.19,1.78)
ETID200	ALED10 +HRT	0.58 (0.09,3.59)	ZOLY5 +TERD20		0.62 (0.04,11.83)	RISD5		2.92 (0.73,14.71)				CLOD800		0.53 (0.03,6.52)
ETID400		1.82 (0.56,6.56)	MIND1		1.34 (0.04,30.41)	IBAD2.5		3.79 (0.87,20.03)				MIND1	ZOLY5	2.60 (0.27,37.58)
ETID400 +HRT		1.55 (0.08,23.02)	IBAM100	IBAD2.5	1.01 (0.54,2.00)	IBAM100		3.59 (0.74,20.91)				CLOD800		2.38 (0.06,85.90)
ETID400 +PHOD2		1.42 (0.36,5.82)	IBAM150		1.07 (0.52,2.31)	IBAM150		3.57 (0.78,19.38)				CLOD800	MIND1	0.93 (0.05,12.06)
RISD2.5		1.02 (0.19,5.29)	ZOLY5		0.84 (0.29,2.82)	IBAQ3		2.42 (0.46,14.56)						
RISD5		1.80 (0.59,5.93)	ZOLY5 +TERD20		0.43 (0.07,2.30)	ZOLY5		2.48 (0.58,13.39)						
IBAD2.5		2.31 (0.71,8.04)	MIND1		0.88 (0.07,7.59)	ZOLY5 +TERD20		1.30 (0.16,11.36)						
IBAM100		2.20 (0.58,8.71)	IBAM150	IBAM100	1.07 (0.55,1.96)	ETID400 +HRT	ETID400	0.85 (0.04,9.95)						
IBAM150		2.19 (0.63,8.09)	ZOLY5		0.83 (0.29,2.55)	ETID400 +PHOD2		0.78 (0.33,1.81)						
IBAQ3		1.46 (0.36,6.22)	ZOLY5 +TERD20		0.43 (0.06,2.18)	RISD2.5		0.56 (0.13,2.13)						
ZOLY5		1.53 (0.47,5.52)	MIND1		0.88 (0.07,6.76)	RISD5		0.98 (0.51,1.83)						
ZOLY5 +TERD20		0.82 (0.13,5.00)	ZOLY5	IBAM150	0.79 (0.35,1.93)	IBAD2.5		1.25 (0.60,2.69)						
MIND1		1.43 (0.35,5.93)	ZOLY5 +TERD20		0.41 (0.07,1.80)	IBAM100		1.20 (0.46,3.03)						

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
CLOD800		0.94 (0.05,13.03)	MIND1		0.82 (0.07,5.87)	IBAM150		1.18 (0.52,2.69)						
TILM350		1.54 (0.38,6.60)	ZOLY5 +TERD20	ZOLY5	0.50 (0.12,1.74)	IBAQ3		0.80 (0.28,2.40)						
TILM1400		1.04 (0.24,4.52)	MIND1		1.02 (0.09,6.35)	ZOLY5		0.83 (0.40,1.75)						
ETID400	ETID200	3.06 (0.70,17.64)	MIND1	ZOLY5 +TERD20	2.01 (0.15,20.72)	ZOLY5 +TERD20		0.43 (0.08,2.05)						
ETID400 +HRT		2.73 (0.12,44.98)				ETID400 +PHOD2	ETID400 +HRT	0.92 (0.07,18.89)						
ETID400 +PHOD2		2.40 (0.48,14.99)				RISD2.5		0.66 (0.04,17.28)						
RISD2.5		1.74 (0.53,6.28)				RISD5		1.13 (0.09,22.45)						
RISD5		3.02 (0.77,15.11)				IBAD2.5		1.46 (0.12,30.00)						
IBAD2.5		3.90 (0.92,20.88)				IBAM100		1.40 (0.11,31.06)						
IBAM100		3.72 (0.77,21.98)				IBAM150		1.37 (0.11,28.77)						
IBAM150		3.70 (0.85,20.32)				IBAQ3		0.96 (0.07,22.22)						
IBAQ3		2.45 (0.50,14.94)				ZOLY5		0.97 (0.08,19.84)						
ZOLY5		2.59 (0.62,14.03)				ZOLY5 +TERD20		0.52 (0.03,13.95)						
ZOLY5 +TERD20		1.38 (0.18,12.00)				RISD2.5	ETID400 +PHOD2	0.73 (0.16,3.07)						
MIND1		2.45 (0.48,14.16)				RISD5		1.26 (0.51,3.00)						
CLOD800		1.53 (0.09,32.35)				IBAD2.5		1.61 (0.62,4.33)						
TILM350		2.58 (0.52,16.10)				IBAM100		1.52 (0.50,4.78)						
TILM1400		1.73 (0.32,11.36)				IBAM150		1.52 (0.55,4.24)						
ETID400 +HRT	ETID400	0.85 (0.05,9.63)				IBAQ3		1.04 (0.30,3.54)						
ETID400 +PHOD2		0.78 (0.33,1.79)				ZOLY5		1.06 (0.41,2.81)						
RISD2.5		0.56 (0.13,2.02)				ZOLY5 +TERD20		0.55 (0.10,3.05)						
RISD5		0.99 (0.50,1.87)				RISD5	RISD2.5	1.74 (0.50,6.49)						
IBAD2.5		1.27 (0.60,2.74)				IBAD2.5		2.22 (0.60,9.22)						
IBAM100		1.20 (0.46,3.13)				IBAM100		2.13 (0.50,9.80)						
IBAM150		1.20 (0.53,2.75)				IBAM150		2.10 (0.53,9.06)						
IBAQ3		0.79 (0.28,2.32)				IBAQ3		1.43 (0.31,7.10)						
ZOLY5		0.84 (0.40,1.80)				ZOLY5		1.48 (0.39,6.12)						
ZOLY5 +TERD20		0.45 (0.09,2.01)				ZOLY5 +TERD20		0.78 (0.12,5.44)						
MIND1		0.78 (0.26,2.24)				IBAD2.5	RISD5	1.28 (0.73,2.43)						
CLOD800		0.50				IBAM100		1.22						

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
		(0.03,5.71)						(0.54,2.84)						
TILM350		0.84 (0.29,2.34)				IBAM150		1.21 (0.62,2.44)						
TILM1400		0.56 (0.18,1.70)				IBAQ3		0.82 (0.32,2.21)						
ETID400 +PHOD2	ETID400 +HRT	0.92 (0.07,16.80)				ZOLY5		0.84 (0.49,1.56)						
RISD2.5		0.64 (0.05,13.00)				ZOLY5 +TERD20		0.45 (0.09,1.94)						
RISD5		1.14 (0.10,21.09)				IBAM100	IBAD2.5	0.95 (0.48,1.87)						
IBAD2.5		1.49 (0.13,26.50)				IBAM150		0.95 (0.51,1.74)						
IBAM100		1.42 (0.12,26.84)				IBAQ3		0.64 (0.30,1.38)						
IBAM150		1.41 (0.12,26.07)				ZOLY5		0.66 (0.33,1.33)						
IBAQ3		0.94 (0.07,18.06)				ZOLY5 +TERD20		0.35 (0.07,1.58)						
ZOLY5		0.98 (0.08,18.74)				IBAM150	IBAM100	1.00 (0.50,1.97)						
ZOLY5 +TERD20		0.53 (0.03,12.81)				IBAQ3		0.67 (0.24,1.88)						
MIND1		0.90 (0.07,18.66)				ZOLY5		0.70 (0.28,1.74)						
CLOD800		0.60 (0.01,24.69)				ZOLY5 +TERD20		0.37 (0.07,1.86)						
TILM350		0.99 (0.08,19.01)				IBAQ3	IBAM150	0.68 (0.26,1.84)						
TILM1400		0.66 (0.05,13.40)				ZOLY5		0.70 (0.32,1.53)						
RISD2.5	ETID400 +PHOD2	0.72 (0.15,3.06)				ZOLY5 +TERD20		0.37 (0.07,1.76)						
RISD5		1.27 (0.51,3.08)				ZOLY5	IBAQ3	1.03 (0.37,2.85)						
IBAD2.5		1.63 (0.63,4.38)				ZOLY5 +TERD20		0.54 (0.09,2.89)						
IBAM100		1.54 (0.51,4.84)				ZOLY5 +TERD20	ZOLY5	0.52 (0.12,2.03)						
IBAM150		1.53 (0.56,4.38)												
IBAQ3		1.02 (0.31,3.50)												
ZOLY5		1.08 (0.41,2.84)												
ZOLY5 +TERD20		0.58 (0.10,3.10)												
MIND1		1.00 (0.29,3.38)												
CLOD800		0.65 (0.04,8.12)												
TILM350		1.08 (0.33,3.62)												
TILM1400		0.72 (0.21,2.56)												
RISD5	RISD2.5	1.74 (0.56,6.67)												
IBAD2.5		2.26 (0.65,9.06)												

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
IBAM100		2.16 (0.53,9.61)												
IBAM150		2.14 (0.59,8.97)												
IBAQ3		1.42 (0.34,6.80)												
ZOLY5		1.50 (0.43,6.11)												
ZOLY5 +TERD20		0.80 (0.12,5.60)												
MIND1		1.39 (0.33,6.68)												
CLOD800		0.90 (0.05,15.67)												
TILM350		1.49 (0.36,7.30)												
TILM1400		0.99 (0.23,5.23)												
IBAD2.5	RISD5	1.29 (0.73,2.38)												
IBAM100		1.22 (0.55,2.83)												
IBAM150		1.22 (0.63,2.45)												
IBAQ3		0.81 (0.32,2.12)												
ZOLY5		0.85 (0.49,1.58)												
ZOLY5 +TERD20		0.45 (0.10,1.98)												
MIND1		0.80 (0.30,2.03)												
CLOD800		0.52 (0.04,5.93)												
TILM350		0.85 (0.34,2.20)												
TILM1400		0.57 (0.22,1.54)												
IBAM100	IBAD2.5	0.95 (0.47,1.85)												
IBAM150		0.95 (0.51,1.71)												
IBAQ3		0.63 (0.30,1.32)												
ZOLY5		0.66 (0.32,1.34)												
ZOLY5 +TERD20		0.35 (0.07,1.59)												
MIND1		0.61 (0.21,1.69)												
CLOD800		0.40 (0.03,4.58)												
TILM350		0.67 (0.25,1.79)												
TILM1400		0.44 (0.15,1.25)												
IBAM150	IBAM100	1.00 (0.50,1.96)												
IBAQ3		0.66												

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
		(0.25,1.83)												
ZOLY5		0.70 (0.28,1.76)												
ZOLY5 +TERD20		0.37 (0.07,1.90)												
MIND1		0.65 (0.19,2.09)												
CLOD800		0.42 (0.03,5.30)												
TILM350		0.70 (0.22,2.23)												
TILM1400		0.47 (0.14,1.58)												
IBAQ3	IBAM150	0.66 (0.26,1.73)												
ZOLY5		0.70 (0.32,1.53)												
ZOLY5 +TERD20		0.37 (0.08,1.77)												
MIND1		0.65 (0.21,1.91)												
CLOD800		0.42 (0.03,4.94)												
TILM350		0.70 (0.24,2.02)												
TILM1400		0.47 (0.15,1.43)												
ZOLY5	IBAQ3	1.06 (0.37,2.88)												
ZOLY5 +TERD20		0.56 (0.09,2.95)												
MIND1		0.98 (0.27,3.33)												
CLOD800		0.63 (0.04,8.04)												
TILM350		1.06 (0.31,3.58)												
TILM1400		0.71 (0.19,2.52)												
ZOLY5 +TERD20	ZOLY5	0.53 (0.13,1.97)												
MIND1		0.93 (0.33,2.54)												
CLOD800		0.60 (0.04,6.91)												
TILM350		1.00 (0.37,2.67)												
TILM1400		0.67 (0.23,1.94)												
MIND1	ZOLY5 +TERD20	1.75 (0.34,9.88)												
CLOD800		1.13 (0.06,18.84)												
TILM350		1.89 (0.35,10.72)												
TILM1400		1.26 (0.23,7.34)												
CLOD800	MIND1	0.65 (0.04,8.65)												

Baseline denominator			Low risk of bias			Five major bisphosphonates			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
TILM350		1.08 (0.32,3.77)												
TILM1400		0.72 (0.19,2.68)												
TILM350	CLOD800	1.65 (0.13,26.65)												
TILM1400		1.10 (0.08,18.16)												
TILM1400	TILM350	0.67 (0.25,1.79)												

TRT=treatment of interest, REF=reference treatment, PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year, TERD20=teriparatide 20 µg/day, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Sensitivity analyses for non-vertebral fracture (primary and secondary after re-classification using 2.5 SD) with comparisons to subgroup analyses

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ALED5	PBO	0.60 (0.31,1.16)	ALED5	PBO	0.60 (0.31,1.16)	ALED5	PBO	1.28 (0.59,2.59)	ALED5	PBO	1.27 (0.57,2.58)
ALED5+ALFD1		0.39 (0.13,1.19)	ALED5+ALFD1		0.39 (0.13,1.21)	ALED10		0.87 (0.49,1.47)	ALED10		0.82 (0.43,1.24)
ALED10		0.75 (0.54,0.99)	ALED10		0.77 (0.56,1.02)	ETID400		0.51 (0.14,1.69)	ETID400		0.51 (0.14,1.66)
ALED10+HRT		0.45 (0.13,1.42)	ALED10+HRT		0.45 (0.14,1.40)	RISD2.5		0.41 (0.08,1.66)	RISD2.5		0.39 (0.08,1.57)
ETID200		0.25 (0.01,2.51)	ETID200		0.28 (0.02,2.47)	RISD5		0.65 (0.20,2.03)	RISD5		0.65 (0.21,1.87)
ETID400		0.99 (0.51,1.88)	ETID400		0.98 (0.50,1.89)	IBAM150		0.96 (0.11,8.04)	IBAM150		0.92 (0.15,5.05)
ETID400+HRT		0.68 (0.03,9.60)	ETID400+HRT		0.80 (0.05,7.82)	ZOLY5		0.26 (0.01,2.39)	ZOLY5		0.28 (0.02,2.64)
ETID400+PHOD2		0.71 (0.30,1.71)	ETID400 +PHOD2		0.72 (0.30,1.67)	ALED10	ALED5	0.68 (0.29,1.67)	ALED10	ALED5	0.64 (0.27,1.48)
RISD2.5		0.45 (0.02,6.25)	RISD2.5		0.51 (0.03,6.59)	ETID400		0.40 (0.09,1.67)	ETID400		0.40 (0.09,1.73)
RISD5		0.84 (0.57,1.13)	RISD5		0.85 (0.57,1.14)	RISD2.5		0.33 (0.06,1.61)	RISD2.5		0.31 (0.05,1.60)
IBAD2.5		1.06 (0.61,1.78)	IBAD2.5		1.07 (0.61,1.82)	RISD5		0.51 (0.13,2.01)	RISD5		0.51 (0.13,1.90)
IBAM100		0.99 (0.44,2.22)	IBAM100		1.01 (0.43,2.23)	IBAM150		0.76 (0.08,7.31)	IBAM150		0.73 (0.11,4.90)
IBAM150		0.97 (0.49,1.91)	IBAM150		1.00 (0.49,1.98)	ZOLY5		0.20 (0.01,2.15)	ZOLY5		0.22 (0.01,2.57)
IBAQ3		0.67 (0.26,1.67)	IBAQ3		0.68 (0.26,1.70)	ETID400	ALED10	0.59 (0.15,2.19)	ETID400	ALED10	0.62 (0.16,2.37)
ZOLY5		0.73 (0.43,1.26)	ZOLY5		0.73 (0.43,1.24)	RISD2.5		0.48 (0.09,2.12)	RISD2.5		0.48 (0.09,2.24)

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**
ZOLY5+TERD20		0.39 (0.08,1.63)	ZOLY5+TERD20		0.38 (0.08,1.63)	RISD5		0.75 (0.21,2.65)	RISD5		0.80 (0.23,2.67)
MIND1		0.55 (0.22,1.31)	MIND1		0.55 (0.22,1.34)	IBAM150		1.12 (0.12,9.98)	IBAM150		1.15 (0.18,6.81)
CLOD800		0.60 (0.02,6.96)	CLOD800		0.68 (0.02,7.53)	ZOLY5		0.30 (0.01,2.97)	ZOLY5		0.35 (0.02,3.47)
TILM350		0.70 (0.28,1.66)	TILM350		0.71 (0.29,1.68)	RISD2.5	ETID400	0.81 (0.11,5.37)	RISD2.5	ETID400	0.78 (0.10,5.44)
TILM1400		0.48 (0.17,1.21)	TILM1400		0.48 (0.18,1.22)	RISD5		1.28 (0.24,7.11)	RISD5		1.26 (0.24,6.48)
ALED5+ALFD1	ALED5	0.65 (0.26,1.58)	ALED5+ALFD1	ALED5	0.66 (0.26,1.63)	IBAM150		1.89 (0.16,23.2)	IBAM150		1.85 (0.23,15.37)
ALED10		1.24 (0.60,2.58)	ALED10		1.29 (0.62,2.62)	ZOLY5		0.50 (0.02,6.84)	ZOLY5		0.54 (0.03,7.78)
ALED10+HRT		0.75 (0.19,2.90)	ALED10+HRT		0.77 (0.19,2.81)	RISD5	RISD2.5	1.57 (0.35,8.30)	RISD5	RISD2.5	1.59 (0.36,8.62)
ETID200		0.41 (0.02,4.43)	ETID200		0.47 (0.03,4.64)	IBAM150		2.37 (0.17,34.7)	IBAM150		2.38 (0.24,24.64)
ETID400		1.65 (0.65,4.12)	ETID400		1.65 (0.64,4.18)	ZOLY5		0.61 (0.02,9.45)	ZOLY5		0.69 (0.03,11.73)
ETID400+HRT		1.12 (0.05,17.18)	ETID400+HRT		1.33 (0.08,13.70)	IBAM150	RISD5	1.49 (0.12,17.0)	IBAM150	RISD5	1.46 (0.17,10.93)
ETID400+PHOD2		1.18 (0.39,3.46)	ETID400+PHOD2		1.21 (0.39,3.54)	ZOLY5		0.40 (0.02,5.08)	ZOLY5		0.43 (0.02,5.70)
RISD2.5		0.74 (0.03,10.96)	RISD2.5		0.85 (0.04,12.33)	ZOLY5	IBAM150	0.25 (0.01,6.67)	ZOLY5	IBAM150	0.29 (0.01,5.62)
RISD5		1.38 (0.66,2.88)	RISD5		1.41 (0.65,2.84)						
IBAD2.5		1.76 (0.74,4.04)	IBAD2.5		1.78 (0.75,4.17)						
IBAM100		1.64 (0.57,4.74)	IBAM100		1.68 (0.57,4.77)						
IBAM150		1.61 (0.61,4.18)	IBAM150		1.67 (0.62,4.38)						
IBAQ3		1.12 (0.35,3.51)	IBAQ3		1.12 (0.36,3.49)						
ZOLY5		1.21 (0.52,2.87)	ZOLY5		1.22 (0.52,2.84)						
ZOLY5+TERD20		0.64 (0.12,3.16)	ZOLY5+TERD20		0.64 (0.12,3.11)						
MIND1		0.91 (0.33,2.54)	MIND1		0.92 (0.33,2.53)						
CLOD800		0.98 (0.03,12.84)	CLOD800		1.12 (0.03,14.26)						
TILM350		1.17 (0.39,3.57)	TILM350		1.18 (0.40,3.52)						
TILM1400		0.79 (0.25,2.54)	TILM1400		0.81 (0.25,2.53)						
ALED10	ALED5+ALFD1	1.91 (0.60,6.10)	ALED10	ALED5+ALFD1	1.97 (0.60,6.27)						
ALED10+HRT		1.15 (0.21,5.97)	ALED10+HRT		1.18 (0.21,5.58)						
ETID200		0.64 (0.03,7.70)	ETID200		0.71 (0.04,8.47)						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ETID400		2.52 (0.70,9.14)	ETID400		2.51 (0.66,9.13)						
ETID400+HRT		1.75 (0.07,30.75)	ETID400+HRT		2.01 (0.10,24.67)						
ETID400+PHOD2		1.81 (0.46,7.42)	ETID400+PHOD2		1.85 (0.43,7.36)						
RISD2.5		1.13 (0.04,19.43)	RISD2.5		1.30 (0.06,21.64)						
RISD5		2.14 (0.67,6.87)	RISD5		2.15 (0.63,6.74)						
IBAD2.5		2.69 (0.77,9.20)	IBAD2.5		2.73 (0.78,9.32)						
IBAM100		2.53 (0.63,10.05)	IBAM100		2.57 (0.63,10.22)						
IBAM150		2.49 (0.68,9.23)	IBAM150		2.56 (0.66,9.37)						
IBAQ3		1.71 (0.40,7.49)	IBAQ3		1.73 (0.40,7.39)						
ZOLY5		1.87 (0.55,6.55)	ZOLY5		1.86 (0.53,6.35)						
ZOLY5+TERD20		1.00 (0.15,6.36)	ZOLY5+TERD20		0.98 (0.15,6.11)						
MIND1		1.39 (0.37,5.49)	MIND1		1.41 (0.36,5.41)						
CLOD800		1.53 (0.04,23.78)	CLOD800		1.66 (0.05,25.37)						
TILM350		1.78 (0.44,7.54)	TILM350		1.80 (0.44,7.45)						
TILM1400		1.22 (0.27,5.26)	TILM1400		1.22 (0.28,5.21)						
ALED10+HRT	ALED10	0.60 (0.18,1.89)	ALED10+HRT	ALED10	0.59 (0.18,1.82)						
ETID200		0.34 (0.01,3.36)	ETID200		0.37 (0.03,3.31)						
ETID400		1.32 (0.65,2.70)	ETID400		1.28 (0.62,2.63)						
ETID400+HRT		0.92 (0.04,13.06)	ETID400+HRT		1.04 (0.06,10.30)						
ETID400+PHOD2		0.95 (0.38,2.42)	ETID400+PHOD2		0.93 (0.37,2.28)						
RISD2.5		0.60 (0.02,8.56)	RISD2.5		0.66 (0.04,8.62)						
RISD5		1.12 (0.71,1.71)	RISD5		1.09 (0.68,1.67)						
IBAD2.5		1.41 (0.80,2.54)	IBAD2.5		1.39 (0.76,2.53)						
IBAM100		1.32 (0.58,3.03)	IBAM100		1.31 (0.56,3.00)						
IBAM150		1.30 (0.67,2.57)	IBAM150		1.30 (0.64,2.62)						
IBAQ3		0.89 (0.34,2.34)	IBAQ3		0.88 (0.34,2.31)						
ZOLY5		0.97 (0.54,1.86)	ZOLY5		0.94 (0.53,1.75)						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ZOLY5+TERD20		0.52 (0.11,2.32)	ZOLY5+TERD20		0.50 (0.11,2.19)						
MIND1		0.74 (0.28,1.85)	MIND1		0.71 (0.28,1.85)						
CLOD800		0.80 (0.02,9.67)	CLOD800		0.88 (0.03,9.85)						
TILM350		0.94 (0.37,2.38)	TILM350		0.92 (0.37,2.33)						
TILM1400		0.64 (0.23,1.74)	TILM1400		0.63 (0.23,1.66)						
ETID200	ALED10+HRT	0.58 (0.02,7.37)	ETID200	ALED10+HRT	0.62 (0.04,7.45)						
ETID400		2.19 (0.57,9.02)	ETID400		2.15 (0.58,8.35)						
ETID400+HRT		1.47 (0.06,33.97)	ETID400+HRT		1.76 (0.08,21.52)						
ETID400+PHOD2		1.58 (0.37,7.07)	ETID400+PHOD2		1.57 (0.39,7.03)						
RISD2.5		1.02 (0.03,17.98)	RISD2.5		1.11 (0.06,19.18)						
RISD5		1.85 (0.56,6.44)	RISD5		1.84 (0.56,6.24)						
IBAD2.5		2.34 (0.66,8.70)	IBAD2.5		2.36 (0.68,8.77)						
IBAM100		2.20 (0.54,9.35)	IBAM100		2.22 (0.54,9.16)						
IBAM150		2.16 (0.58,8.51)	IBAM150		2.20 (0.60,8.46)						
IBAQ3		1.48 (0.34,6.91)	IBAQ3		1.48 (0.35,6.87)						
ZOLY5		1.62 (0.46,6.09)	ZOLY5		1.60 (0.47,5.94)						
ZOLY5+TERD20		0.85 (0.13,5.72)	ZOLY5+TERD20		0.85 (0.12,5.31)						
MIND1		1.21 (0.28,5.55)	MIND1		1.21 (0.28,5.63)						
CLOD800		1.33 (0.03,22.25)	CLOD800		1.42 (0.04,21.75)						
TILM350		1.56 (0.36,7.23)	TILM350		1.56 (0.37,6.60)						
TILM1400		1.06 (0.24,4.91)	TILM1400		1.06 (0.24,4.74)						
ETID400	ETID200	3.95 (0.35,96.79)	ETID400	ETID200	3.50 (0.36,46.76)						
ETID400+HRT		2.79 (0.06,121.20)	ETID400+HRT		2.80 (0.07,89.51)						
ETID400+PHOD2		2.83 (0.23,71.96)	ETID400+PHOD2		2.57 (0.25,37.37)						
RISD2.5		1.79 (0.46,7.50)	RISD2.5		1.81 (0.50,7.57)						
RISD5		3.30 (0.32,84.45)	RISD5		2.95 (0.33,37.96)						
IBAD2.5		4.23 (0.39,98.69)	IBAD2.5		3.75 (0.40,51.28)						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
IBAM100		4.02 (0.34,101.30)	IBAM100		3.55 (0.34,50.44)						
IBAM150		3.96 (0.35,95.79)	IBAM150		3.55 (0.35,48.66)						
IBAQ3		2.69 (0.22,67.62)	IBAQ3		2.41 (0.23,36.88)						
ZOLY5		2.91 (0.28,72.38)	ZOLY5		2.57 (0.28,35.45)						
ZOLY5+TERD20		1.49 (0.11,41.49)	ZOLY5+TERD20		1.38 (0.10,25.11)						
MIND1		2.20 (0.18,55.18)	MIND1		1.97 (0.19,28.76)						
CLOD800		2.35 (0.04,119.30)	CLOD800		2.34 (0.04,76.13)						
TILM350		2.80 (0.23,78.52)	TILM350		2.51 (0.24,37.08)						
TILM1400		1.95 (0.15,55.90)	TILM1400		1.71 (0.17,24.05)						
ETID400+HRT	ETID400	0.69 (0.04,9.99)	ETID400+HRT	ETID400	0.81 (0.04,8.12)						
ETID400+PHOD2		0.72 (0.30,1.70)	ETID400+PHOD2		0.73 (0.31,1.70)						
RISD2.5		0.44 (0.02,7.01)	RISD2.5		0.52 (0.03,7.35)						
RISD5		0.84 (0.40,1.74)	RISD5		0.85 (0.40,1.75)						
IBAD2.5		1.06 (0.47,2.50)	IBAD2.5		1.08 (0.47,2.59)						
IBAM100		1.00 (0.36,2.86)	IBAM100		1.02 (0.36,2.95)						
IBAM150		0.98 (0.38,2.51)	IBAM150		1.01 (0.39,2.69)						
IBAQ3		0.67 (0.22,2.13)	IBAQ3		0.68 (0.22,2.19)						
ZOLY5		0.74 (0.32,1.71)	ZOLY5		0.74 (0.32,1.72)						
ZOLY5+TERD20		0.39 (0.07,1.92)	ZOLY5+TERD20		0.39 (0.08,1.92)						
MIND1		0.56 (0.18,1.59)	MIND1		0.56 (0.18,1.71)						
CLOD800		0.60 (0.02,7.93)	CLOD800		0.70 (0.02,8.24)						
TILM350		0.71 (0.23,2.12)	TILM350		0.72 (0.24,2.17)						
TILM1400		0.48 (0.15,1.49)	TILM1400		0.49 (0.15,1.55)						
ETID400+PHOD2	ETID400+HRT	1.05 (0.07,22.94)	ETID400+PHOD2	ETID400+HRT	0.90 (0.08,17.33)						
RISD2.5		0.64 (0.01,36.83)	RISD2.5		0.66 (0.02,33.59)						
RISD5		1.23 (0.09,26.08)	RISD5		1.05 (0.10,19.08)						
IBAD2.5		1.57 (0.10,33.53)	IBAD2.5		1.35 (0.13,23.69)						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
IBAM100		1.47 (0.09,33.47)	IBAM100		1.26 (0.12,23.40)						
IBAM150		1.44 (0.09,31.90)	IBAM150		1.27 (0.12,23.32)						
IBAQ3		1.00 (0.06,22.84)	IBAQ3		0.86 (0.08,15.91)						
ZOLY5		1.08 (0.07,23.48)	ZOLY5		0.92 (0.09,16.67)						
ZOLY5+TERD20		0.57 (0.02,17.64)	ZOLY5+TERD20		0.50 (0.03,11.39)						
MIND1		0.82 (0.05,19.24)	MIND1		0.68 (0.06,14.86)						
CLOD800		0.80 (0.01,47.10)	CLOD800		0.83 (0.02,33.40)						
TILM350		1.04 (0.06,22.87)	TILM350		0.88 (0.08,17.83)						
TILM1400		0.70 (0.04,15.49)	TILM1400		0.60 (0.05,12.61)						
RISD2.5	ETID400+PHOD2	0.62 (0.02,10.19)	RISD2.5	ETID400+PHOD2	0.71 (0.04,10.47)						
RISD5		1.18 (0.45,3.00)	RISD5		1.17 (0.47,2.96)						
IBAD2.5		1.49 (0.53,4.17)	IBAD2.5		1.49 (0.55,4.16)						
IBAM100		1.40 (0.41,4.61)	IBAM100		1.40 (0.44,4.66)						
IBAM150		1.37 (0.45,4.05)	IBAM150		1.39 (0.46,4.25)						
IBAQ3		0.94 (0.26,3.44)	IBAQ3		0.94 (0.27,3.42)						
ZOLY5		1.03 (0.37,2.90)	ZOLY5		1.01 (0.38,2.82)						
ZOLY5+TERD20		0.54 (0.09,2.95)	ZOLY5+TERD20		0.53 (0.09,2.94)						
MIND1		0.78 (0.22,2.63)	MIND1		0.77 (0.22,2.75)						
CLOD800		0.84 (0.02,12.11)	CLOD800		0.94 (0.03,12.01)						
TILM350		0.99 (0.28,3.41)	TILM350		0.99 (0.29,3.42)						
TILM1400		0.67 (0.18,2.47)	TILM1400		0.67 (0.19,2.41)						
RISD5	RISD2.5	1.88 (0.13,49.76)	RISD5	RISD2.5	1.65 (0.12,30.22)						
IBAD2.5		2.39 (0.16,62.23)	IBAD2.5		2.12 (0.15,38.21)						
IBAM100		2.26 (0.14,62.94)	IBAM100		1.99 (0.14,38.33)						
IBAM150		2.20 (0.14,58.95)	IBAM150		1.97 (0.14,37.54)						
IBAQ3		1.51 (0.09,43.80)	IBAQ3		1.34 (0.09,28.32)						
ZOLY5		1.64 (0.11,44.88)	ZOLY5		1.44 (0.11,27.47)						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ZOLY5+TERD20		0.86 (0.04,26.83)	ZOLY5+TERD20		0.75 (0.04,18.22)						
MIND1		1.25 (0.07,35.63)	MIND1		1.08 (0.07,21.22)						
CLOD800		1.34 (0.02,82.47)	CLOD800		1.23 (0.02,55.36)						
TILM350		1.58 (0.09,48.26)	TILM350		1.40 (0.09,26.76)						
TILM1400		1.09 (0.06,33.67)	TILM1400		0.94 (0.07,18.58)						
IBAD2.5	RISD5	1.26 (0.69,2.41)	IBAD2.5	RISD5	1.27 (0.70,2.49)						
IBAM100		1.18 (0.50,2.91)	IBAM100		1.19 (0.50,2.94)						
IBAM150		1.16 (0.56,2.51)	IBAM150		1.19 (0.56,2.62)						
IBAQ3		0.80 (0.30,2.21)	IBAQ3		0.80 (0.31,2.23)						
ZOLY5		0.86 (0.49,1.74)	ZOLY5		0.86 (0.48,1.71)						
ZOLY5+TERD20		0.47 (0.09,2.08)	ZOLY5+TERD20		0.46 (0.10,2.07)						
MIND1		0.66 (0.25,1.67)	MIND1		0.65 (0.25,1.74)						
CLOD800		0.72 (0.02,8.80)	CLOD800		0.81 (0.03,9.19)						
TILM350		0.84 (0.32,2.18)	TILM350		0.84 (0.34,2.22)						
TILM1400		0.57 (0.20,1.60)	TILM1400		0.58 (0.21,1.59)						
IBAM100	IBAD2.5	0.94 (0.47,1.89)	IBAM100	IBAD2.5	0.94 (0.46,1.89)						
IBAM150		0.92 (0.48,1.75)	IBAM150		0.93 (0.48,1.81)						
IBAQ3		0.63 (0.29,1.36)	IBAQ3		0.63 (0.30,1.33)						
ZOLY5		0.69 (0.33,1.50)	ZOLY5		0.68 (0.32,1.46)						
ZOLY5+TERD20		0.37 (0.07,1.74)	ZOLY5+TERD20		0.36 (0.07,1.70)						
MIND1		0.52 (0.18,1.45)	MIND1		0.52 (0.18,1.47)						
CLOD800		0.57 (0.02,7.14)	CLOD800		0.64 (0.02,7.30)						
TILM350		0.66 (0.23,1.85)	TILM350		0.66 (0.24,1.82)						
TILM1400		0.45 (0.15,1.33)	TILM1400		0.45 (0.15,1.31)						
IBAM150	IBAM100	0.98 (0.48,1.99)	IBAM150	IBAM100	1.00 (0.48,2.02)						
IBAQ3		0.67 (0.24,1.91)	IBAQ3		0.67 (0.24,1.87)						
ZOLY5		0.74 (0.28,1.99)	ZOLY5		0.72 (0.29,1.97)						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ZOLY5+TERD20		0.39 (0.06,2.13)	ZOLY5+TERD20		0.39 (0.07,1.95)						
MIND1		0.55 (0.16,1.85)	MIND1		0.55 (0.17,1.87)						
CLOD800		0.61 (0.02,8.01)	CLOD800		0.67 (0.02,8.57)						
TILM350		0.70 (0.22,2.35)	TILM350		0.70 (0.22,2.34)						
TILM1400		0.48 (0.13,1.70)	TILM1400		0.48 (0.14,1.67)						
IBAQ3	IBAM150	0.69 (0.26,1.88)	IBAQ3	IBAM150	0.68 (0.25,1.81)						
ZOLY5		0.75 (0.32,1.82)	ZOLY5		0.73 (0.31,1.75)						
ZOLY5+TERD20		0.40 (0.07,2.04)	ZOLY5+TERD20		0.39 (0.07,1.93)						
MIND1		0.57 (0.18,1.72)	MIND1		0.55 (0.18,1.73)						
CLOD800		0.62 (0.02,7.87)	CLOD800		0.68 (0.02,8.31)						
TILM350		0.72 (0.24,2.21)	TILM350		0.71 (0.24,2.17)						
TILM1400		0.49 (0.15,1.59)	TILM1400		0.48 (0.15,1.53)						
ZOLY5	IBAQ3	1.09 (0.38,3.23)	ZOLY5	IBAQ3	1.08 (0.37,3.14)						
ZOLY5+TERD20		0.58 (0.10,3.21)	ZOLY5+TERD20		0.56 (0.10,3.24)						
MIND1		0.82 (0.22,2.94)	MIND1		0.82 (0.22,2.99)						
CLOD800		0.90 (0.03,12.59)	CLOD800		0.99 (0.03,12.47)						
TILM350		1.06 (0.28,3.74)	TILM350		1.05 (0.29,3.77)						
TILM1400		0.71 (0.18,2.68)	TILM1400		0.71 (0.19,2.67)						
ZOLY5+TERD20	ZOLY5	0.54 (0.12,2.06)	ZOLY5+TERD20	ZOLY5	0.53 (0.12,2.02)						
MIND1		0.76 (0.26,2.05)	MIND1		0.75 (0.27,2.12)						
CLOD800		0.82 (0.02,10.20)	CLOD800		0.93 (0.03,10.64)						
TILM350		0.96 (0.34,2.62)	TILM350		0.97 (0.36,2.63)						
TILM1400		0.66 (0.21,1.92)	TILM1400		0.66 (0.22,1.91)						
MIND1	ZOLY5+TERD20	1.41 (0.25,8.74)	MIND1	ZOLY5+TERD20	1.42 (0.27,8.44)						
CLOD800		1.58 (0.03,27.23)	CLOD800		1.73 (0.05,27.32)						
TILM350		1.79 (0.32,11.19)	TILM350		1.85 (0.35,10.37)						
TILM1400		1.23 (0.22,7.97)	TILM1400		1.26 (0.23,7.18)						
CLOD800	MIND1	1.09 (0.03,15.39)	CLOD800	MIND1	1.20						

Subgroup (Secondary)			Sensitivity (Secondary)			Subgroup (Primary)			Sensitivity (Primary)		
TRT	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**
					(0.04,15.55)						
TILM350		1.27 (0.36,4.63)	TILM350		1.29 (0.37,4.34)						
TILM1400		0.87 (0.24,3.30)	TILM1400		0.87 (0.25,3.16)						
TILM350	CLOD800	1.16 (0.09,42.46)	TILM350	CLOD800	1.07 (0.08,33.84)						
TILM1400		0.79 (0.06,30.89)	TILM1400		0.74 (0.05,24.32)						
TILM1400	TILM350	0.68 (0.25,1.88)	TILM1400	TILM350	0.68 (0.25,1.80)						

TRT=treatment of interest, REF=reference treatment, PBO=placebo, ALED5=alendronate 5 mg/day or 35 mg/week, ALFD1=alfacalcidol 1 µg/d, ALED10=alendronate 10 mg/day or 70 mg/week, HRT=hormone replacement therapy, ETID200=etidronate 200 mg/day, ETID400=etidronate 400 mg/day, PHOD2=phosphate 2 g/day, RISD2.5=risedronate 2.5 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5 =ibandronate 2.5 mg/day, IBAM100=ibandronate 100 mg/month, IBAM150=ibandronate 150 mg/month, IBAQ3= ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year, TERD20=teriparatide 20 µg/day, MIND1=minodronate 1 mg/day, CLOD800=clodronate 800 mg/day, TILM350=tiludronate 350 mg/month, TILM1400=tiludronate 1400 mg/month.

Sensitivity analyses for hip fracture

Baseline denominator			Low risk of bias			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**	**TRT**	**REF**	**OR (95% CrI)**
ALED10	PBO	0.67 (0.44,1.00)	ALED10	PBO	0.68 (0.41,1.07)	ALED10	PBO	0.59 (0.32,1.00)	ALED10	PBO	0.57 (0.31,0.97)
ETID400		0.85 (0.14,4.75)	ETID400		2.02 (0.11,63.7)	RISD5		0.72 (0.40,1.31)	ETID400		2.06 (0.12,58.3)
RISD5		0.72 (0.43,1.21)	ZOLY5		0.58 (0.29,1.12)	IBAD2.5		1.45 (0.38,6.09)	IBAD2.5		1.48 (0.36,6.40)
IBAD2.5		1.43 (0.38,5.39)	ETID400	ALED10	2.98 (0.15,93.4)	ZOLY5		0.57 (0.34,0.95)	ETID400	ALED10	3.69 (0.21,115)
IBAQ3		0.50 (0.02,7.61)	ZOLY5		0.85 (0.38,2.00)	RISD5	ALED10	1.23 (0.58,2.98)	IBAD2.5		2.60 (0.60,12.7)
ZOLY5		0.55 (0.35,0.87)	ZOLY5	ETID400	0.29 (0.01,6.0)	IBAD2.5		2.48 (0.59,11.8)	IBAD2.5	ETID400	0.74 (0.02,16.0)
ETID400	ALED10	1.27 (0.19,7.69)				ZOLY5		0.97 (0.47,2.17)			
RISD5		1.08 (0.56,2.11)				IBAD2.5	RISD5	2.00 (0.46,9.60)			
IBAD2.5		2.10 (0.56,8.59)				ZOLY5		0.79 (0.36,1.71)			
IBAQ3		0.75 (0.02,11.8)				ZOLY5	IBAD2.5	0.40 (0.08,1.66)			
ZOLY5		0.83 (0.45,1.50)									
RISD5	ETID400	0.85 (0.14,5.82)									
IBAD2.5		1.68 (0.19,14.8)									
IBAQ3		0.61 (0.01,15.1)									
ZOLY5		0.65 (0.11,4.35)									
IBAD2.5	RISD5	1.95 (0.48,8.20)									
IBAQ3		0.69 (0.02,11.0)									
ZOLY5		0.77 (0.38,1.47)									

Baseline denominator			Low risk of bias			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
IBAQ3	IBAD2.5	0.36 (0.01,3.70)									
ZOLY5		0.39 (0.10,1.54)									
ZOLY5	IBAQ3	1.10 (0.07,38.4)									

TRT=treatment of interest, REF=reference treatment, PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, RISD5=risedronate 5 mg/day or 35 mg/week or 150 mg/month, IBAD2.5=ibandronate 2.5 mg/day, IBAQ3=ibandronate 3 mg/3 months, ZOLY5=zoledronic acid 5 mg/year.

Sensitivity analyses for wrist fracture

Baseline denominator			Low risk of bias			Fracture as efficacy outcome			Bisphosphonate naïve		
TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)	TRT	REF	OR (95% CrI)
ALED10	PBO	0.81 (0.44,1.49)	ALED10	PBO	0.85 (0.35,1.86)	ALED10	PBO	0.84 (0.35,1.78)	ALED10	PBO	0.52 (0.31,0.87)
ETID400		0.92 (0.09,8.81)	ZOLY5		0.21 (0.01,2.05)	RISD5		0.63 (0.19,2.19)			
RISD5		0.60 (0.20,1.67)	ZOLY5	ALED10	0.26 (0.01,2.86)	RISD5	ALED10	0.75 (0.18,3.60)			
ZOLY5		0.19 (0.02,1.08)									
ETID400	ALED10	1.14 (0.10,11.90)									
RISD5		0.73 (0.20,2.48)									
ZOLY5		0.23 (0.02,1.33)									
RISD5	ETID400	0.65 (0.05,7.94)									
ZOLY5		0.20 (0.01,3.76)									
ZOLY5	RISD5	0.32 (0.03,2.56)									

TRT=treatment of interest, REF=reference treatment, PBO=placebo, ALED10=alendronate 10 mg/day or 70 mg/week, ETID400=etidronate 400 mg/day, RISD5=risedronate 5 mg/day, ZOLY5=zoledronic acid 5 mg/year.