EFFICACY AND SAFETY OF BISPHOSPHONATES FOR FRACTURE PREVENTION IN OSTEOPOROSIS

SYSTEMATIC REVIEWS AND INDIRECT TREATMENT COMPARISONS

MAURICA MAHER

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in
Partial fulfillment of the requirements for the MSc degree in Epidemiology

Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

ABSTRACT

Osteoporosis is a growing cause of morbidity and mortality in aging populations worldwide, especially in postmenopausal women. Bisphosphonates are widely prescribed for fracture prevention in osteoporosis. Meta-analyses have been performed for alendronate, risedronate, and etidronate, examining their effectiveness versus placebo in fracture prevention. Total withdrawals and adverse event withdrawals were examined as safety outcomes. Systematic reviews were performed for two other bisphosphonates, ibandronate and zoledronic acid and the results combined with previously obtained data for the other bisphosphonates. Indirect treatment comparisons of the drugs against each other and versus placebo were performed using Bayesian and frequentist methods. Both types of analyses yielded almost identical results: zoledronic acid and alendronate were the most effective bisphosphonates for preventing vertebral fractures. No differences were found regarding withdrawals. Subgroup analyses found that fracture prevention was generally more effective with longer therapy (greater than or longer than 3 years).

ACKNOWLEDGEMENTS

I have many individuals to thank for their assistance and support throughout this project. First, Dr. George Wells, Professor in the Department of Epidemiology and Community Medicine, and Director of the Cardiovascular Research Methods Centre at the Ottawa Heart Institute, provided me the opportunity to work on this project, guided me through all the stages of design and conduct, and was always available to provide his expertise and encouragement.

I would like to thank as well Tamara Rader of the University of Ottawa for conducting the literature reviews which initiated this project. Joan Petersen and Shu-Ching Hsieh of the Cardiovascular Research Methods Centre acted as independent assessors along with me to review the literature search results, assess studies for inclusion, and extract data. Chris Cameron and Lily Chen, also of the Cardiovascular Research Methods Centre, were invaluable in their teaching on the use of software analysis programs and I was very grateful for their patience during this process.

Finally, I would like to thank Dr. Geoff Dunkley, Dr. Branda Wilson, and Jennifer Collins of the Public Health and Preventive Medicine Residency program at the University of Ottawa for their support during this thesis project.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

TABLE OF ABBREVIATIONS

BMD. Bone mineral density.

BMI. Body mass index.

BUGS. Bayesian Inference Using Gibbs Sampling.

Ca. Calcium.

CI. Confidence Interval.

CrI. Credibility Interval.

CTX. Type I collagen.

DXA. Dual Energy X-ray Absorptimetry.

EMA. European Medicines Agency.

FDA. Food and Drug Administration.

GLMM. Generalized linear mixed model.

iv. Intravenous administration.

MTC. Multiple treatment comparison.

NMA. Network meta-analysis.

NNT. Number needed to treat.

OR. Odds Ratio.

PICO. Population, intervention, comparator, outcome.

po. Oral administration.

RCT. Randomized control trial.

ROB. Risk of bias.

SD. Standard deviation.

1 INTRODUCTION

1.1 Rationale

Osteoporosis is a serious health issue in the elderly, especially post-menopausal women, as its associated fragility fractures result in substantial morbidity and mortality[1]. Osteoporosis increases the risk of bone fracture[2]. The number of seniors with osteoporosis is expected to continue to grow over the coming decades in Canada and the United States[3], making the cost of osteoporosis and its complications an increasing burden to the health care system. Fragility fractures (fractures that result from minimal trauma or a fall from standing height or less) are frequently associated with the beginning of a loss of function and independence and can have a substantial impact on the quality of life for those affected and their caregivers[4]. Thus the prevention of osteoporosis and its associated fragility fractures can have many benefits at individual, population, and societal levels.

The most frequently used medications for fracture prevention in postmenopausal women with osteoporosis are bisphosphonates, which are synthetic analogues of a naturally-occurring compound[5]. Initially these products were clinically used for their ability to inhibit calcification; subsequently they were investigated and approved for conditions in which there is an increase in bone resorption, which leads to a weakening of bone and increased fracture risks[6]. In addition to being used in osteoporosis, bisphosphonates are also used in other bone metabolism disorders such as Paget's disease and hypercalcemia of cancer. Given the increasing number of seniors that are being treated with bisphosphonates for extended periods of time, evaluating the benefits and harms of these products is important so that patients and health care professionals can make informed decisions about their use.

Worldwide there are five commonly used bisphosphonates for the prevention of fractures in women with postmenopausal osteoporosis: etidronate, alendronate, risedronate, ibandronate, and zoledronic acid[7]. The comparator for these products in clinical trials

conducted for regulatory approval was placebo (plus calcium and vitamin D). Although the early bisphosphonates were approved using bone mineral density as the outcome, regulators now require demonstration of decreased fracture risk for approval[8,9]. Information on the comparative efficacy of the different bisphosphonates in osteoporosis is limited as there have been few head-to-head trials examining the differences between bisphosphonates, and only one has used fracture as an endpoint[10]. In addition, fracture prevention trials are lengthy (1 year or longer) and therefore resource- intensive. Consequently it is unlikely that there will be enough direct evidence comparing the bisphosphonates that are authorized for the treatment of osteoporosis. Meta-analyses have been performed for some individual bisphosphonates and published as Cochrane reviews, combining data from trials that used a placebo as a comparator[11-13]. Neither ibandronate nor zoledronic acid have been the subject of such reviews. Previous indirect treatment comparisons have not made use of newer network meta-analytic techniques or been conducted with the most recently available data. Although bisphosphonates are generally considered to have a positive safety record, there have been concerns regarding withdrawals and adherence to long-term therapy, in addition to uncommon adverse events such as atypical fractures and osteonecrosis of the jaw.

The rationale of this thesis was to summarize current efficacy and safety data for bisphosphonates by updating previously obtained data and combining their results by means of indirect treatment comparisons. As no similar review had previously been done for ibandronate or zolendronic acid, separate systematic reviews of these products were required. It is anticipated that this information will assist patients and professionals in selecting appropriate therapies and identify areas that need further research.

1.2 Thesis objectives

The objectives of this thesis are:

1) To assess the clinical efficacy and safety of ibandronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women

compared with untreated women (usually treated with calcium and vitamin D) over a time period of at least one year.

2) To assess the clinical efficacy and safety of zoledronic acid in the primary and secondary prevention of osteoporotic fractures in postmenopausal women compared with untreated women (usually treated with calcium and vitamin D) over a time period of at least one year.
3) To compare the clinical efficacy and safety of alendronate, risedronate, etidronate, zoledronic acid, and ibandronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women using indirect treatment comparison methodologies.

1.3 Chapter description

Chapter 2 provides an overview of the pathophysiology of osteoporosis, its epidemiology, and the burden of disease. A description of the different bisphosphonates and their mechanism of action are provided. Other therapies that are currently in use for osteoporosis with different mechanisms of action are also briefly discussed.

Chapter 3 presents the methods and results for the systematic review and meta-analysis of the efficacy and safety of ibandronate used in the treatment of osteoporosis. Efficacy outcomes were the number of vertebral, non-vertebral, hip and wrist fractures. Safety outcomes were total number of withdrawals from trials as well as withdrawals due to adverse events.

Chapter 4 presents the methods and results for the systematic review of the efficacy and safety of zoledronic acid. The outcomes assessed were the same as those examined for ibandronate.

Chapter 5 discusses the different methodological approaches for performing indirect treatment comparisons, including the two which were used for the comparison of the five

bisphosphonates to each other as well as placebo (or calcium and vitamin D). Efficacy and safety outcomes, as well as subgroup and sensitivity analyses are presented.

Chapter 6 presents closing remarks regarding network meta-analysis and the alignment of results from this thesis with results from the literature.

2 BISPHOSPHONATE THERAPY IN OSTEOPOROSIS

2.1 Introduction to osteoporosis

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength which predisposes those affected to an increased risk of fractures[14]. In the clinical setting it is defined by either low bone mineral density or a history of fragility fracture[15]. Bone strength is dependent on bone density and bone quality. Bone quality involves the architecture, turnover, accumulation of damage such as micro-fractures, and mineralization. Bone density accounts for 70% of bone strength and is expressed as grams of mineral per area or as volume.

Osteoporosis is a heterogeneous condition that can arise through multiple causes including hormone loss, iatrogenic causes, physical limitations such as immobility or lack of weight bearing activity, or genetic disorders. Primary osteoporosis is seen as a result of aging as a consequence of a decrease in bone quality and quantity that occurs in both men and women beginning in midlife[14]. Bone loss is more rapid in women following menopause due to a loss of endogenous estrogen[16]. Secondary osteoporosis results from effects on bone from other medical disorders such as genetic disorders (osteogenesis imperfecta), rheumatological conditions(arthritides), endocrine disorders (hyperthryroidism, hyperparathyroidism, diabetes), inadequate nutrition via malabsorption (such as Crohn's disease) or diet (vitamin D), kidney disease, liver disease, as well as being a result of certain medication use such as glucocorticoids[14,17].

2.2 Diagnosis of osteoporosis

Osteoporosis is commonly detected by evaluating bone density through the measurement of bone mineral density (BMD) of the spine or hip by Dual Energy X-ray Absorptimetry (DXA)[18] and this technique is also used to evaluate a patient's response to therapy. The BMD is presented as gram per centimeter squared, and is compared to the mean value for a young adult population and a "T-score" is calculated, being the number of standard

deviations (SDs) above or below the mean BMD for young adults[19]. In 1994 the World Health Organization Study Group on osteoporosis defined the disease as "a hip BMD level of more than 2.5 SDs below the mean BMD for young, white, adult women"[20]. Since the creation of this definition, newer research has indicated that although bone mass or density is an important factor contributing to fracture risk, other elements such as quality of bone are important[21]. Osteopenia is defined as a T-score between -1.0 and -2.5.

Osteoporosis can also be diagnosed on a history of a previous osteoporotic or fragility fracture. These are fractures that result from minimal trauma or a fall from standing height or less, and generally would not occur in individuals with normal bone[15]. Such fractures are a risk factor for future fractures and indicate a need for assessment and treatment where appropriate.

2.3 Epidemiology and consequences of osteoporosis

Osteoporosis and its resultant fragility fractures are important public health issues[1] that primarily impact the elderly. It has been estimated that 1 in 4 women in Canada and 1 in 8 men have osteoporosis[18]. The population of Canada is aging and it is expected that 27% of the population will be over 65 years of age by 2056, compared to 13.2% in 2005[22]. As a result, the prevalence of osteoporosis and its consequences are expected to increase dramatically over the next few decades[3]. In the United States, projections estimate that >14 million people will have osteoporosis in 2020[23]. It is estimated that there are approximately 9 million osteoporotic fractures worldwide annually, and that over half of these occur in Europe and the Americas[17].

Osteoporosis is an important risk factor for bone fracture, and patients with osteoporosis have a lifetime risk of fracture of greater than 40%[2]. Osteoporosis is frequently diagnosed after the first clinical fracture has occurred, because bone loss occurs slowly and is asymptomatic in the early stages[24,25]. The overall lifetime risk of fracture in Caucasian women has been estimated to be 50%[26,27] and osteoporotic fractures make up 80% of all fractures in women over 50 years of age[28].

Osteoporotic fractures can be classified as vertebral and non-vertebral (non-spine) fractures. Non-vertebral fractures include hip, forearm, wrist, and others (e.g. humerus, pelvis, ribs, lower leg). Vertebral fractures are the most common type of osteoporotic fractures[17] and occur in 20% of postmenopausal women[29]. These types of fractures are often asymptomatic and may go undetected[19].

The morbidity, mortality, and financial consequences of osteoporotic fractures in the elderly are considerable. There is a significantly increased risk of death after hip and vertebral fractures[30,31], which persists for 1 to 2 years after the event. Hip fractures are the most serious type of osteoporotic fracture and are associated with permanent disability, institutionalization, and increased mortality. Twenty percent of patients sustaining a hip fracture will die within 12 months[4]. Vertebral fractures are also associated with excess mortality, and are second to hip fractures in this respect[32,33]. Vertebral fractures are predictive for subsequent vertebral, hip and other non-vertebral fractures[34]. For all types of fractures – hip, vertebral and other non-vertebral – mortality increases with age[1]. It is estimated that women lose 11.2 years of life after a hip fracture and 2 years after a vertebral fracture[30]. Hip fractures in particular can result in a significant change in functional status, and 20% of women will require long-term care after such a fracture[4]. The economic burden of osteoporotic fractures in the United States in 2005 was estimated to be 17 billion for more than 2 million incident fractures and is estimated to increase to 25 billion per year by 2025[35]. In Canada, it has been estimated that in 2008 the acute care cost of osteoporosis was 1.2 billion dollars, with 618.6 million being due to the cost of osteoporosis-related hip fractures[36].

2.4 Pathophysiology of osteoporosis

Bone is a living tissue that is constantly renewed, or remodeled, throughout life. This is performed by two types of processes, bone resorption (degradation) and bone formation[6,7]. Bone resorption is a function of cells known as osteoclasts while bone formation is performed by osteoblasts. The non-cellular components of bone are a mineral phase embedded within an organic phase which is mostly type I collagen. The

mineral phase consists of calcium and phosphate that form a crystalline structure known as hydroxyapatite, which is deposited in between the collagen fibers. The two-phase system of bone construction provides it with considerable strength that allows it to withstand mechanical stress.

Normally bone resorption and formation are coupled processes, with resorption being followed by formation[29]. Osteoclast precursors are activated by the binding of receptor activator of nuclear factor κB ligand (RANKL) to their RANK receptors. This stimulates the precursors to form multinucleated cells that then differentiate to form osteoclasts which then attach to the bone surface. After attachment, they secrete hydrochloric acid to dissolve bone mineral and cathepsin K, which dissolves the bone matrix. Following resorption, mononuclear cells prepare the surface for the work of osteoblasts, which deposit layers of bone collagen matrix. After the mineralization of the matrix, some osteoblast are incorporated into the bone matrix and become osteocytes that are connected to the surface of the bone and with each other[21].

In postmenopausal osteoporosis bone resorption by osteoclasts is increased, leading to a loss of bone mass, weakened bone architecture, and an increased fracture risk[37]. After menopause, there is a decrease in estrogen production, which inhibits osteoclast activity. The resulting estrogen deprivation contributes to a loss of bone mass as the osteoclasts resorb bone[21]. In addition, lower levels of estrogen are associated with decreased intestinal calcium absorption and increasing urinary calcium loss[38]. As a result there is rapid bone loss after menopause, with women losing about 12% of bone mass in the 5-7 years after menopause[39].

2.4 Mechanism of action of bisphosphonates

Bisphosphonates are stable analogues of inorganic pyrophosphate, a naturally occurring polyphosphate that inhibits calcification in soft tissues by binding to hydroxyapatite[40,5]. Bisphosphonates, like pyrophosphate, have a high affinity for bone mineral and prevent calcification[6]. In addition, bisphosphonates inhibit the dissolution of hydroxyapatite

crystals in bone[41,42] and inhibit bone resorption by osteoclasts in animals. This high affinity for bone relative to other tissues results in a high concentration of bisphosphonates being deposited in the skeleton. The ability of bisphosphonates to decrease bone resorption in conditions where there is excessive or imbalanced skeletal remodeling led to the development of these compounds as a treatment for osteoporosis of various origins including fibrous dysplasia, osteogenesis imperfecta, Paget's disease of bone, hypercalcemia, and skeletal involvement with malignancy[37,43]. The first bisphosphonate that was investigated for therapeutic purposes was etidronate, which was found to be effective for calcification disorders such as fibrodysplasia ossificans progressive and Paget's disease[44,45]. They have since become the treatment of choice for bone diseases characterized by excessive osteoclast activity[6].

Bisphosphonates are widely thought to be most active against mature osteoclasts[7]. After bisphosphonates are bound to bone mineral, they are released during resorption and internalized by osteoclasts, where they induce several types of changes that can result in cell death or a decrease in cell functions[46]. The anti-resorptive capacity of bisphosphonates is related to their chemical structure and varying the R_2 side chain of these molecules can alter their potency as much as 40-fold[47-49]. Simple bisphosphonates are those that lack a nitrogen atom in their side chain, such as etidronate. They are metabolized in cells to non-hydrolysable ATP analogues, which induce osteoclast apoptosis and inhibit bone resorption[50], probably by inhibiting intracellular ATP-dependent enzymes[51]. Nitrogen-containing bisphosphonates include alendronate, risedronate, ibandronate, and zoledronic acid. These compounds act on several enzymes in the mevalonate pathway, but their major target is the inhibition of the enzyme farnesyl pyrophosphate synthase, whereby they prevent the prenylation of proteins needed for osteoclast survival[6,52]. Each bisphosphonate is unique with respect to its ability to bind to bone and it biochemical effects on cells. The rank order of binding affinity to the major bisphosphonates used in postmenopausal osteoporosis is zoledronic acid >alendronate > ibandronate > risedronate > etidronate[53]. In terms of ability to inhibit farnesyl pyrophosphate synthase the order is zoledronic acid > risedronate > ibandronate >

alendronate. These features contribute to the different pharmacologic and clinical effects of these molecules.

2.6 Bisphosphonates used in the treatment of osteoporosis

There are at least eleven bisphosphonates that have received approval for different clinical indications in various countries, however not all have been authorized for the treatment of post-menopausal osteoporosis[7]. Other indications for bisphosphonates include genetic disorders, Paget's disease, and hypercalcemia of malignancy. Although theoretically all the bisphosphonates could be used in any of these conditions characterized by excessive bone resorption, not all have undergone the clinical development process for each condition. The bisphosphonates that are widely used in postmenopausal osteoporosis are etidronate, alendronate, risedronate, ibandronate, and zoledronic acid[7]. Minodronate is authorized in Japan for this indication[54]. Bisphosphonates have become the most commonly used treatments in postmenopausal osteoporosis[15,55].

Etidronate was the first bisphosphonate to be used in humans as an inhibitor of calcification, and was the first used in the treatment of post-menopausal osteoporosis[56], although it was not approved for this use until the 1990's. In Canada, etidronate was the first bisphosphonate approved in osteoporosis in 1995, followed by alendronate (1996), risedronate (1996), and zoledronic acid (2005)[57]. Ibandronate is not marketed in Canada, but is available in the European Union[58] and the United States[59]. Etidronate, alendronate and risedronate are available in oral forms, ibandronate is available in both oral and intravenous forms, while zoledronic acid is only available intravenously. Table 1 shows the commonly used bisphosphonates used in the treatment of osteoporosis in Canada and the United States.

Table 1. Bisphosphonates authorized for prevention and treatment of osteoporosis in Canada and the United States.

Bisphosphonate	Canada		United States		Dose and Route of Administration	
	Prev	**Treat**	**Prev**	**Treat**	**Prev**	**Treat**
Alendronate	Yes	Yes	Yes	Yes	5 mg po daily	10 mg po daily, 70 mg weekly
Etidronate	Yes	Yes	No	No	400 mg po daily for 14 days of a 90-day cycle[1]	400 mg po daily for 14 days of a 90-day cycle
Ibandronate	No	No	Yes	Yes	2.5 mg po daily, 150 mg po monthly	2.5 mg po daily, 150 mg po monthly, 3 mg iv every 3 months
Risedronate	Yes	Yes	Yes	Yes	5 mg po daily, 35 mg po weekly	5 mg po daily, 35 mg po weekly 75 mg po twice per month, 150 mg po monthly
Zoledronic Acid	Yes	Yes	Yes	Yes	5 mg iv annually	5 mg iv annually

Note: Prev, prevention; Treat, treatment; po, oral; iv, intravenous.
[1]Etidronate is a cyclical regimen given in 90-days cycles, with etidronate taken for the first 14 days followed by calcium carbonate for the next 76 days.

2.7 Efficacy of bisphosphonates

The efficacy of bisphosphonates has been demonstrated in randomized placebo-controlled trials using various endpoints including reduction in the incidence of fractures and biochemical markers such as CTX and BMD. Currently, however, regulatory agencies require that reduction in fracture risk be the primary endpoint for regulatory approval[8,9,10]. According to the European Medicines Agency, BMD is an important predictor of osteoporotic fractures in postmenopausal women without a previous fracture and although it may be the primary end point in exploratory studies it is not an appropriate surrogate for fracture reduction for market authorization. For medicines that have already been granted an indication based on anti-fracture efficacy, an extension of the indication can be considered for a new dose, route of administration or formulation on the basis of the demonstration of non-inferiority in terms of BMD changes.

All of the commonly used bisphosphonates for osteoporosis have been shown to decrease vertebral fracture risk in randomized controlled trials[29], however, not all have been

demonstrated to decrease a reduction in hip and other non-vertebral fractures. Non-vertebral fractures occur less frequently than vertebral fractures[8], and not all studies were powered to detect a difference with respect to non-vertebral fractures. The bisphosphonates that have been shown to decrease hip fracture risk in randomized controlled trials versus placebo are alendronate and zoledronic acid.

The efficacies of alendronate, risedronate, and etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women have all been the subject of individual Cochrane reviews[11-13]. Studies that included women whose bone density was within 2 SD of the mean or those in which the prevalence of vertebral fracture at baseline was less than 20% were considered to be primary prevention studies. Trials were classified as secondary prevention trials if they included women with bone density that was less than 2 SD values below mean bone mass, if they included only women who had a previous vertebral fracture, or if the average age of participants was greater than 62 years. These reviews found that these three drugs had different efficacy profiles for primary and secondary prevention of different types of fractures (Tables 2 and 3). Ibandronate and zoledronic acid have not yet been the subject of a similar review.

Table 2. Efficacy of selected bisphosphonates compared to placebo for primary prevention of osteoporotic fractures in postmenopausal women[11-13].

Outcome measure	**Alendronate 10 mg/day for 1-4 years**	**Risedronate 5 mg/day for 2 years**	**Etidronate 400 mg/day for 1-3 years**
Vertebral fractures RR (95% CI) Study quality	 0.55 (0.38, 0.80) moderate	 0.97 (0.42, 2.25) low	 3.03 (0.32, 28.44) Very low
Hip fractures RR (95% CI) Study quality	 0.79 (0.44, 1.44) low	 Not estimable [2] Very low	 No trials available

[1] RR (95% CI), relative risk and 95% confidence interval.[2] Only one study was available.

Table 3. Efficacy of selected bisphosphonates compared to placebo for secondary prevention of osteoporotic fractures in postmenopausal women[11-13].

Outcome measure	Alendronate 10 mg/day for 1-3 years	Risedronate 5 mg/day for 3 years	Etidronate 400 mg/day for 1-3 years
Vertebral fractures			
RR (95% CI)	0.55 (0.43, 0.69)	0.61 (0.50, 0.76)	0.53 (0.32, 0.87)
Study quality	Moderate	Moderate	moderate
Hip fractures			
RR (95% CI)	0.47 (0.26, 0.85)	0.74 (0.59, 0.94)	1.20 (0.37, 3.88)
Study quality	moderate	Moderate	Low

[1] RR (95% CI), relative risk and 95% confidence interval.

Comparing the efficacy of the different bisphosphonates in reduction of fracture risk has been hampered by a lack of head-to-head trials using fracture risk as a primary endpoint[55,60], although some active comparator trials have compared changes in BMD and CTX[61-63]. Systematic reviews have found only one head-to-head trial of bisphosphonates that was designed to compare fracture outcomes[10,64]. Some trials have been conducted as open-label studies as there are blinding challenges with the various dosage forms and dosing schedules (some products are administered orally daily, weekly, or monthly, while others are given intravenously yearly or quarterly). Some trials have reported fracture incidence as a secondary or safety endpoint or as part of overall adverse event reporting. However, this requires the patient to present with clinical symptoms and as a result asymptomatic vertebral fractures may go undetected. The incidence of "non-vertebral" fracture determination from published studies can also be challenging as the definition varies from trial to trial, may or may not include hip fracture, and may not be fully explained in publications.

Number needed to treat (NNT) calculations have been used as one method for comparing the efficacy of bisphosphonates in fracture prevention (compared with placebo) to each other and other treatments for osteoporosis that promote bone formation, such as strontium. Results from one analysis found that the NNT to prevent one vertebral fracture over 3 years for alendronate ibandronate, risedronate and zoledronic acid ranged from 14 to 21[65]. Prevention of hip fracture over the same time period was calculated to be 91 for alendronate, risedronate and zoledronic acid. Table 4 provides a summary of published

NNT values for the most commonly used bisphosphonates[66]. These findings must to be interpreted with caution as the severity of disease in the study populations were variable; for example, some studies included women with osteopenia while others restricted inclusion to women with a BMD < 2.5 and prevalent vertebral fractures[60]. As a result, a drug may have one NNT value for those at a lower risk for fracture, for example in women with osteopenia only, and a different NNT value for those at higher risk.

Table 4. Number needed to treat values for fracture prevention in osteoporosis with bisphosphonate use[66].

Bisphosphonate	Vertebral Fractures	Non-Vertebral Fractures	Hip Fractures
Alendronate	14 – 60	39-68	90-447
Ibandronate	20	N/A	N/A
Risedronate	9 – 20	20-56	91-276
Zoledronic Acid	13	37	91

Note: N/A, not available.

Indirect treatment comparisons can be used to compare the results of treatments through the use of common comparators when there is a lack of available direct, or head-to-head, comparisons[67,68]. These types of analyses are the basis of network meta-analyses techniques that are being more frequently used to compare therapies that are unlikely to be the subjects of randomized controlled trials.

One network meta-analysis[69] has compared zoledronic acid, alendronate, ibandronate, risedronate, and etidronate but this study was subject to several limitations. The inclusion criteria resulted in only 8 studies being included in the analysis, and did not include studies published after November 2007. This analysis found that zoledronic acid use had the greatest reduction in vertebral and hip fractures, and that risedronate use had the greatest reduction in non-vertebral, non-hip fractures. This study report primarily the results of a fixed effects model; the random effects model (now the preferred model for network meta-analysis) estimates produced similar point estimates but wider credibility intervals, which increased the uncertainty of the results.

A subsequent network meta-analysis[70] examined the relative efficacy nine drugs in fracture reduction in post-menopausal women: alendronate, etidronate, ibandronate, risedronate, zoledronic acid, denosumab, raloxifene, strontium, and teriparatide. The last four drugs that were included in this analysis are not bisphosphonates and their clinical effects are through other mechanisms of action. This analysis included 25 studies with bisphosphonates from 1999-2009 and examined vertebral, non-vertebral, hip, and wrist fractures. With respect to the bisphosphonates examined, zoledronic acid was the most efficacious in reducing vertebral fracture risk. Although etidronate appeared the most efficacious bisphosphonate for preventing non-vertebral fractures, the authors expressed concern about this result as etidronate did not have a statistically significant result versus placebo for non-vertebral fractures; in addition the trials were small and this resulted in a small effect size. Zoledronic acid, followed by etidronate and alendronate were found to be the most efficacious at preventing hip fractures, although there were less data available for this analysis.

The most recent network meta-analysis[71] compared the nine drugs included in the 2011 study and the same bisphosphonates (rather than generate odds ratios with credibility intervals, the analytic techniques were adapted to generate relative risks and confidence intervals for comparisons). Compared to placebo, all the agents except for etidronate were effective in reducing the risk of vertebral fractures. Risedronate and zoledronic acid were again found to be effective reducing the risk of non-vertebral and hip fractures, while alendronate was effective in reducing the risk of non-vertebral fractures.

2.8 Safety of bisphosphonates

Since their introduction, concerns have arisen regarding the adverse event profile of bisphosphonates, including irritation of the gastrointestinal tract, osteonecrosis of the jaw, esophageal cancer, atrial fibrillation, and most recently “atypical fractures” such as low energy fractures, fractures of the femur, and pelvic insufficiency fractures[72]. The product monographs for the bisphosphonates marketed in Canada include warning statements regarding these adverse events[73-76]. These safety issues have been identified through

clinical trials, post-market surveillance and reporting, as well as observational studies. Although observational trials are vulnerable to bias and have significant limitations with respect to establishing causality[77], for certain uncommon events they may be the only source of information available, and have been recommended to be included into assessments of harm[78-80].

The safety of bisphosphonates has been discussed in several review articles and specific adverse events have been the subject of observational studies for uncommon and rare adverse events, for example atypical femoral fractures[81,82]. However, there has not been a comparison of the adverse event profile of the different bisphosphonates, making the benefit-risk evaluations of these drugs challenging. The Cochrane reviews of alendronate, etidronate, and risedronate[11-13] did examine the relative risks of withdrawals due to side effects in the included clinical trials, and this is summarized in Table 5.

Table 5. Withdrawals due to side effects of selected bisphosphonates compared with placebo for prevention of osteoporotic fractures in postmenopausal women[11-13].

Outcome Measure	Alendronate 10 mg/day for 1-4 years	Risedronate 5 mg/day for 2 years	Etidronate 400 mg/day for 1-3 years
Withdrawals due to side effects			
RR (95% CI)[1]	0.95 (0.83, 1.09)	0.96 (0.88, 1.05)	0.61 (0.25, 1.49) low
Study quality	Low	low	

[1] RR (95% CI), relative risk and 95% confidence interval.

Withdrawals to due to adverse events or other causes have not been the subject of any of the previously discussed network meta-analyses.

2.9 Other therapies

There are other drugs authorized for the prevention and treatment of post-menopausal osteoporosis in Canada and the United States.

Raloxifene is a selective estrogen receptor modulator (SERM) which is authorized for the prevention and treatment of osteoporosis in post-menopausal women in Canada[83]. It is administered as a daily 60 mg oral doses.

The SERM profile of raloxifene includes estrogen agonist effects on bone. Raloxifene's biological activity is mediated through high affinity binding to estrogen receptors, resulting in the differential expression of several estrogen-regulated genes in different tissues. As described previously, bone undergoes continuous remodeling throughout life. Ovarian estrogen is important for maintaining the balance of bone resorption and formation. After menopause, bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset the increased losses of bone due to resorption. Although raloxifene increases BMD to a lesser extent than estrogen, the effects of raloxifene on bone turnover in postmenopausal women parallel those of estrogen, as shown by studies of bone mineral densitometry, radiocalcium kinetics, bone markers, and bone histomorphometry.

Teriparatide is authorized in Canada for the treatment of postmenopausal women with severe osteoporosis who are at high risk of fracture or who have failed or are intolerant to previous osteoporosis therapy[84]. Teriparatide is administered as a subcutaneous injection into the thigh or abdominal wall at a recommended dosage of 20 mcg once a day.

The biological actions of teriparatide, like those of parathyroid hormone (PTH), are mediated through binding to specific high-affinity cell-surface receptors (PTH is the primary regulator of calcium and phosphate metabolism in bone). Both teriparatide and PTH bind to these receptors with the same affinity and have the same physiological actions on bone. Daily administration of teriparatide stimulates new bone formation by preferentially stimulating the activity of osteoblasts over osteoclasts. This results in an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength.

Denosumab is authorized in Canada for the treatment of postmenopausal women with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture, or multiple risk factors for fracture) or for patients who have failed or are intolerant to other osteoporosis therapies[85]. It is administered as a single subcutaneous injection at a recommended dosage of 60 mg, once every 6 months.

Denosumab is a RANK ligand (RANKL) inhibitor. RANK ligand is essential for the formation, function and survival of osteoclasts, which are responsible for bone resorption and are overactive compared with osteoblasts in post-menopausal women. Denosumab targets and binds with high affinity and specificity to RANKL and as a result prevent the activation of RANK, on the surface of osteoclasts. This interaction inhibits osteoclast formation, function and survival, decreasing bone resorption and increasing bone mass.

3 SYSTEMATIC REVIEW AND META-ANALYSIS OF EFFICACY AND SAFETY OF IBANDRONATE

3.1 Introduction

A systematic review is a method of collecting empirical evidence according to pre-specified eligibility criteria to answer a specific research question, and by doing so minimize bias so that the results are more reliable[86,87]. The Cochrane Handbook for Systematic Reviews of Interventions[88] states that the key elements of such reviews are:

- "a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies."

Systematic reviews provide a means of summarizing the known information about a health care intervention in a manner that is objective, transparent, and reproducible[89], and such reviews are considered to have less bias than narrative reviews.

When appropriate, the data obtained from a systematic review can be analysed using meta-analysis, a statistical method used to summarize the results of independent studies[90]. Meta-analyses can generate more precise estimates than those resulting from individual studies and can provide information about the consistency of results across different studies[88].

The following systematic review and meta-analysis of ibandronate in the treatment of osteoporosis was performed according to the methods described in the Cochrane Handbook[88], and is similar to those previously conducted for alendronate, etidronate, and risedronate[11-13]. Any deviations from recommended methodology are reported.

3.2 Methods

3.2.1 Study inclusion criteria

The PICO (population, intervention, comparator, outcome) criteria outlined below were used to determine if studies were to be included in the review.

- Types of studies

Only randomized controlled trials (RCT) with a duration of at least one year were included.

- Types of participants

Studies that enrolled postmenopausal women were included. Both primary and secondary prevention trials were included to permit comparisons of outcomes by the severity of the condition of the participants. If a trial restricted the population to women whose bone density was at least 2 SD below the peak bone mass or to women who had already experienced a vertebral fracture, it was considered to be a secondary prevention trial (as these are indicators of more advanced bone loss). If the inclusion criteria were not provided or were not clear, a trial was considered to be a primary prevention study if the baseline characteristics indicated that the that the average T-score (and SD) was within 2 SD of the mean or the prevalence of vertebral fractures of the participants at baseline was less than 20%.

- Types of intervention and comparator

Studies that randomized patients to receive ibandronate at any dose and any route of administration or no treatment (including placebo or calcium plus vitamin D) were

included. If the study used calcium and vitamin D controls, the same treatment had to be given concurrently in the ibandronate treatment group(s).

- Types of outcome measures

The efficacy outcome measures of interest were the incidence of fractures (number of women who sustained a fracture), and these were classified by vertebral, non-vertebral, hip and wrist fractures, where possible. Safety outcomes included the total number of withdrawals, number of withdrawals due to adverse events, and number of serious adverse events when available.

3.2.2 Search methods

A computerized search strategy was created with the assistance of an information scientist to incorporate both efficacy and safety outcomes. The following electronic databases where searched through December 12, 2011 using an OVID interface:

- CENTRAL, DARE, HTA Database and NHS EED, The Cochrane Library, 2011
- EMBASE, 1980 to 2011, week 49
- MEDLINE, 1948 to present and In-Process & Other Non-Indexed Citations
- Scopus
- WHO International Clinical Trials Registry Platform

No language limits were applied to the search. The full search strategies are presented in Appendix 1.

In addition, the bibliographies of included articles, relevant systematic and non-systematic reviews were searched for additional references. The websites of the United States Food and Drug Administration and the European Medicines Agency were searched for reviews and other documents relevant to ibandronate. These can be found at:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=BONIVA
and
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000502/human_med_000677.jsp&mid=WC0b01ac058001d124.

3.2.3 Methods of the systematic review

3.2.3.1 Selection of studies

Article titles and abstracts were assessed against the PICO eligibility criteria in an un-blinded standardized manner by two assessors. If there were uncertainties regarding eligibility, these were resolved by discussion and consensus with the thesis supervisor. Any RCT that appeared to potentially meet the review criteria was obtained in full text format, after which the inclusion criteria were applied and a final decision was made concerning eligibility. There was no blinding of articles by study authors or research centres as this has not been demonstrated to appreciably improve the review process, but does increase workload[88].

In the event that there were multiple published reports or outcomes from one study, these publications were linked together and referred to by the included study. The primary study publication was the one used for data extraction. For this review there was no need to perform additional data extraction for the additional publications as they did not contain additional fracture information.

3.2.3.2 Data extraction and management

Data was extracted from each eligible publication using a standardized data abstraction form that was based on the Cochrane Consumer's and Communication Review Group's data extraction template[88].

Information that was extracted included: 1) study design; 2) inclusion criteria and major exclusion criteria; 3) characteristics of participants, including age, country, presence of vertebral fractures, and concomitant medication use; 4) type of intervention including study drug, duration of use, dose, frequency, and route of administration; 5) and outcomes assessed, including number of patients with vertebral, non-vertebral, hip and wrist fractures, total withdrawals, withdrawals due to adverse events, and serious adverse events.

3.2.3.2 Quality assessment

Each included study was assessed for quality using the Cochrane Collaboration's tool[88] for assessing risk of bias (ROB) by two independent assessors. Any uncertainties were discussed until consensus was reached between the assessors and confirmed with the supervisor.

The Cochrane ROB tool examines six separate "domains" with respect to risk of bias: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and "other issues". Each domain is included in a ROB table that includes a description of what was done in the study as well as the assignment of a judgment about the adequacy of the study with respect to minimizing potential sources of bias. Three categories are used regarding ROB: low, high, or unclear. The judgment about ROB is based on the adequacy of the publication in describing how these potential sources of bias were addressed or minimized. Using the RevMan computer program developed by the Cochrane Collaboration, figures and graphs illustrating the ROB can be generated.

As recommended in the Cochrane Handbook, blinding was assessed with respect to the blinding of participants and staff involved in the trial, as well as blinding of the outcome assessors. In addition, blinding was assessed for both objective and subjective outcomes; objective outcomes included those outcomes with objective criteria such as the

assessment of radiographs, while subjective outcomes included outcomes such as adverse events that were not assigned specific criteria.

3.2.3.4 Assessment of heterogeneity

Clinical heterogeneity was assessed by examining the clinical and methodological diversity of the studies. Meta-analyses were only performed if the participant characteristics, interventions, and outcome data of the included studies were assessed as being sufficiently homogenous.

Statistical heterogeneity was assessed through examination of Forest plots to determine if there was an absence of overlap in the confidence intervals that would suggest heterogeneity[88]. Heterogeneity was assessed formally by quantifying the magnitude of inconsistency across studies with the I^2 statistic[90,91]. This statistic indicates the percentage of variability that is due to heterogeneity rather than chance. The I^2 statistic is generally interpreted using a rule of thumb where 25% suggests mild, 50% suggests moderate, and greater than 75% suggests high heterogeneity. Any heterogeneity >50% was to be assessed with sensitivity analysis where possible, for example with respect to study characteristics such as primary or secondary prevention, participant characteristics such as age, trial methodologies, and treatment protocols such as differences in dose and duration of treatment.

3.2.3.5 Data synthesis

Review Manager 5.1 software available from the Cochrane Collaboration (http://ims.cochrane.org/revman) was used for the statistical analyses, according to the guidelines of the Cochrane Handbook[88]. All outcomes of interest were dichotomous and were analyzed using a random and fixed effects models. The random effects model assumes that the studies included have estimated different treatment effects and is the preferred model for such analyses as it is more conservative (as opposed to a fixed-effect

model which assumes that the treatment effect is the same across all studies). Data were pooled for primary and secondary prevention trials, and the risk ratios (RR) of fracture, as well as corresponding 95% confidence intervals, was calculated for vertebral, non-vertebral (non-spine fractures other than hip and wrist, such as shoulder or arm) hip and wrist fractures, where possible. The random effects model was the primary analytical model, and the fixed-effect model was used as a sensitivity analysis.

3.2.3.6 Assessment of publication bias

The potential for publication bias was to be assessed by the creation of funnel plots for each outcome. The bias against the publication of smaller studies that have not found statistically significant effects can lead to an overestimation of treatment effect in a meta-analysis. Funnel plots are one way to potentially detect publication bias. They are visual representations of the estimated intervention effects of each study and the study sizes. Effect estimates are plotted on the horizontal axis and the measure of study size is on the vertical axis, creating a funnel-shaped plot in which the effect estimates from smaller studies scatter more widely at the bottom of the graph, whereas the spread is narrow among the larger studies. Thus the plot resembles an inverted funnel when there is an absence of bias. However, in the case of bias due to unpublished smaller studies, the funnel appears asymmetrical and there is a gap in the shape of the gap. Funnel plot asymmetry can result from other causes than publication bias (small study effects), and these should be examined should asymmetry be detected.

3.2.3.7 Subgroup analyses

Subgroup analyses were planned similar to those that had been performed for the meta-analyses of alendronate, risedronate, and etidronate[11-13] and included primary versus secondary prevention trials, age of participants, treatment duration and treatment dose.

3.2.3.8 Sensitivity analyses

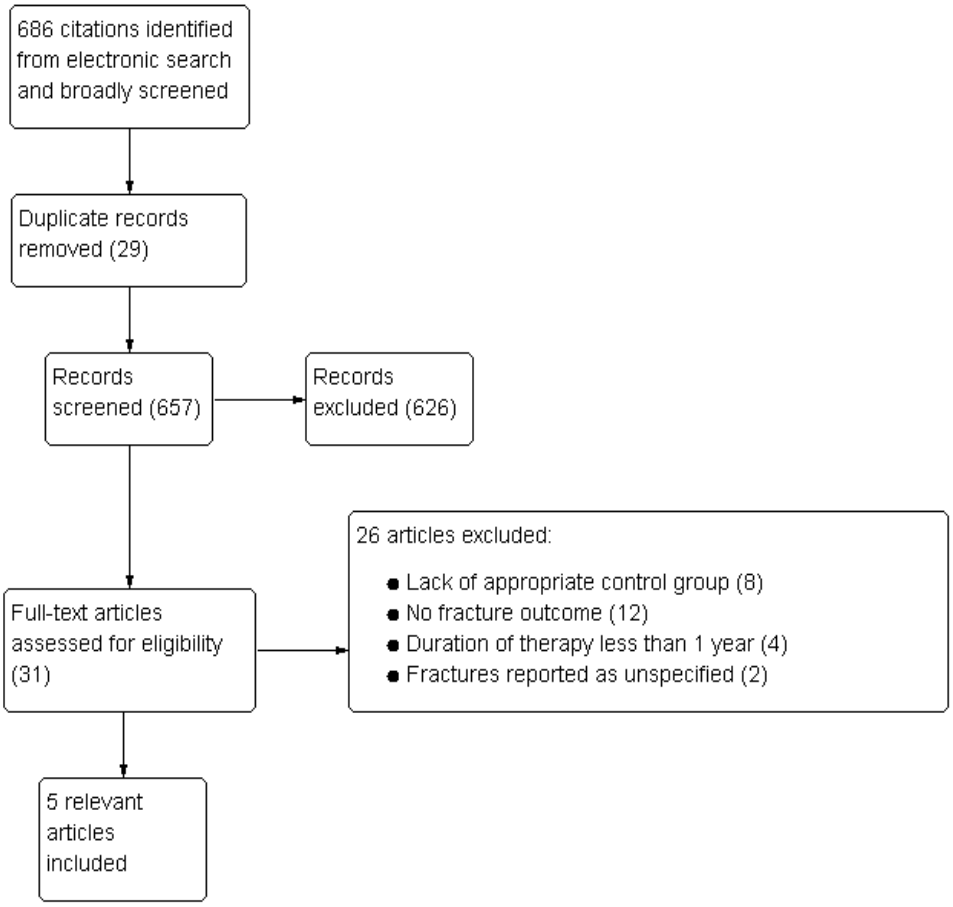
Sensitivity analyses were to be performed examining any difference in results using: 1) baseline denominators versus follow-up denominators; 2) random effects versus fixed-effect models; and 3) baseline vertebral fracture rate.

3.3 Results

3.3.1 Results of the search

The systematic search strategy identified 657 studies of potential interest for the review after the removal of duplicate reports. After inspection of the title and/or abstract, 626 reports were excluded, and as a result the remaining 31 references were screened by reading the full text. Only 3 studies met the original inclusion criteria (ibandronate compared to placebo), however 2 trials were identified that compared ibandronate to another bisphosphonate, alendronate, so a separate analysis was performed to examine these 2 bisphosphonates. The review process is depicted in Figure 1.

Figure 1. Schematic of the review process for ibandronate.



Appendix 2 contains a list of excluded studies and the reasons for exclusion.

3.3.2 Included studies

In total, 3 trials met the original selection criteria for inclusion[118-120]. Two of these trials were secondary fracture prevention trials and contributed 5806 patients[118,119]. The third was a primary prevention trial and contributed 160 patients[120]. Both efficacy and safety outcomes were reported in all trials, but number of patients with new fractures was reported as an efficacy outcome in two trials[118,119] and as a safety outcome in the other trial[120] (change in bone mineral density was the efficacy outcome).

Given the small number of trials that met the original criteria for inclusion, the original search was then examined for head-to-head trials of ibandronate versus other bisphosphonates. This search identified 2 trials that had the same active comparator, alendronate[62,121], and these trials were included in a separate analysis. Both of these trials were secondary prevention trials. One trial contributed 158 participants[121] and the other contributed 1650 participants[62]. Fractures were reported as adverse events (safety outcomes) for both of these trials.

All studies were reported in English. Main characteristics of the included studies are depicted in Appendix 3.

3.3.2.1 Characteristics of the patients

For the two largest trials[118,119] that compared ibandronate to placebo, participants were postmenopausal women who either had prevalent vertebral fractures and a BMD T-score between -2.0 and -5.0 in at least one lumbar vertebra, and were therefore secondary prevention trials. The mean age of women in these studies was between 67 and 69 years. Patients were had received previous treatment with bisphosphonates or those with disorders of bone metabolism were excluded from these studies. The third trial included postmenopausal women who had a BMD T-score between -1.0 and -2.5 who did not have prevalent vertebral fractures (primary prevention)[120]. Women in this trial were younger (mean age 53 years) than in the two larger trials, likely due to the exclusion of women with prevalent fractures and the lower BMD T-score criteria. This trial also excluded women who had previous bisphosphonate treatment (within 2 years), diseases of bone metabolism, and those with major upper gastrointestinal disease (as bisphosphonate use is associated with upper gastrointestinal adverse events such as esophagitis). Concomitant medication use was not reported.

For the two trials that compared ibandronate and alendronate, the participants were postmenopausal women with a BMD T-score lower than -2.0 or between -2.5 and -5.0[62,121]. Both were secondary prevention trials. The mean age of women in these studies

was 65 years. History of bisphosphonate use or diseases of bone metabolism were exclusion criteria for these studies. Concomitant medication use was not reported.

3.3.2.2 Characteristics of the intervention and comparators

In the three trials that compared ibandronate and placebo, patients received either oral or intravenous ibandronate or placebo. All patients received calcium and vitamin D supplements.

The two trials that utilized oral ibandronate provided daily or intermittent ibandronate[118,120]. One trial used a daily dose of ibandronate (2.5 mg, annual cumulative dose of 912.5 mg, intermittent ibandronate (20 mg every other day for 12 doses every 3 months, annual cumulative dose 960 mg), or placebo and had a duration of 3 years[118]. The other oral ibandronate trial provided ibandronate monthly (150 mg, annual cumulative dose of 1800 mg) or placebo for 1 year[120]. The trial that used intravenous ibandronate included three arms that used ibandronate 0.5 mg every 3 months (annual cumulative dose 2 mg), ibandronate 1.0 mg every 3 months (annual cumulative dose 4 mg), or placebo for 3 years[119]. The bioavailability of ibandronate is 0.6% (FDA prescribing information) and can be used to calculate the approximate equivalent intravenous dose for the trials that used oral ibandronate (Table 6).

Table 6. Ibandronate doses and routes of administration used in trials comparing ibandronate to placebo.

Trial	Duration	Ibandronate Doses and Routes of Administration	Annual Cumulative Dose (mg)
Chesnut 2004[118]	3 years	2.5 mg po[1] daily 20 mg po every other day for 12 doses every 3 months	5.5 5.76
Recker 2004[119]	3 y-ears	0.5 mg iv[2] every 3 months 1.0 mg iv every 3 months	2 4
McClung 2009[120]	1 year	150 mg po monthly	10.8

[1]po, oral. [2]iv, intravenous.

Both trials that compared ibandronate and alendronate were 1 year in duration. One trial used intravenous ibandronate at a dose of 2 mg every 3 months (annual cumulative dose of 8 mg)[121], while the other used oral ibandronate at a dose of 150 mg monthly (annual cumulative equivalent dose 10.8 mg)[62]. Both trials used alendronate 70 mg monthly administered orally as a comparator.

3.3.2.3 Characteristics of the outcomes

Two trials that compared ibandronate with placebo had a primary efficacy endpoint of the rate of fractures (number of patients with a new fracture over the course of the trial)[118-119]. Fractures were reported as vertebral, non-vertebral, and in one trial[119] the number of hip fractures was reported. Cumulative incidence (and number of patients) of vertebral fractures was reported for both trials. However only cumulative incidence of non-vertebral fractures was reported for one trial and the number of patients with such fractures was not available[119]. In one trial the non-vertebral fractures were not further categorized[118], thus the number of hip fractures are unknown. The third trial that compared ibandronate and placebo reported fractures as adverse events and all were non-vertebral in nature[120].

The two studies that compared ibandronate and alendronate reported fractures as adverse events[62,121]. One study reported fractures as vertebral and non-vertebral[62], while the other study reported vertebral, non-vertebral, and hip fractures[121].

3.3.3 Quality assessment

The assessment of study quality yielded a low risk of bias in most domains. Adequate sequence generation was not addressed in 4 studies, and allocation concealment was not addressed in any of the 5 studies and this resulted in "unclear" assessments in these areas. The risk of bias was "unclear" regarding the blinding of objective outcome assessment in 1 study and regarding the blinding of subjective outcome assessments in 4 studies. One

study had a “high” risk of bias in the blinding of subjective outcome assessments. One study had a “high” risk of bias with respect to incomplete reporting of outcomes.

The results of the risk of bias assessment using the tools provided in RevMan are shown in Figures 2 and 3.

Figure 2. Risk of bias graph for included ibandronate studies[62,118-121] (Assessor’s judgments about each risk of bias item presented as percentages across all included studies).

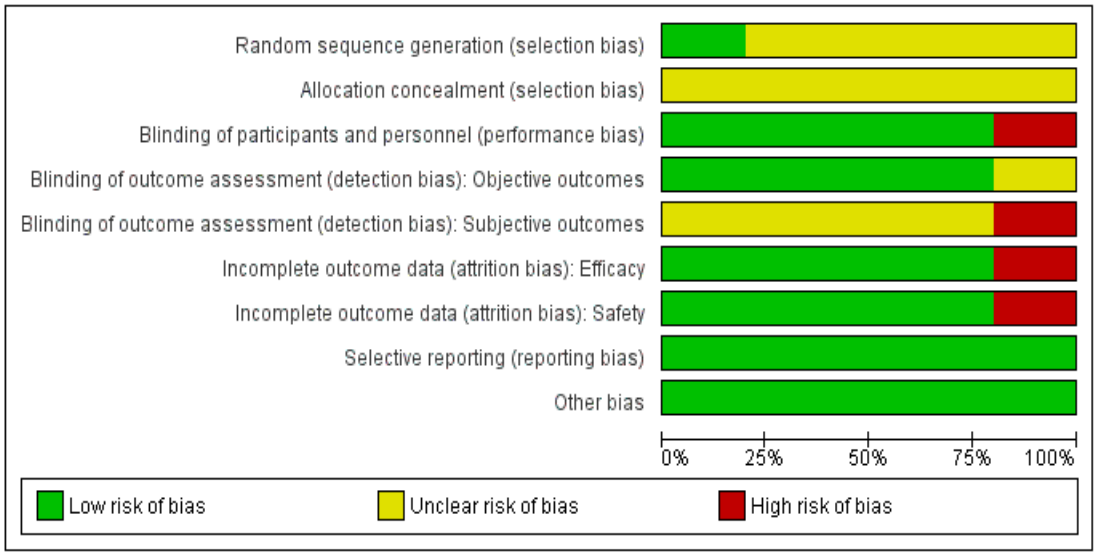
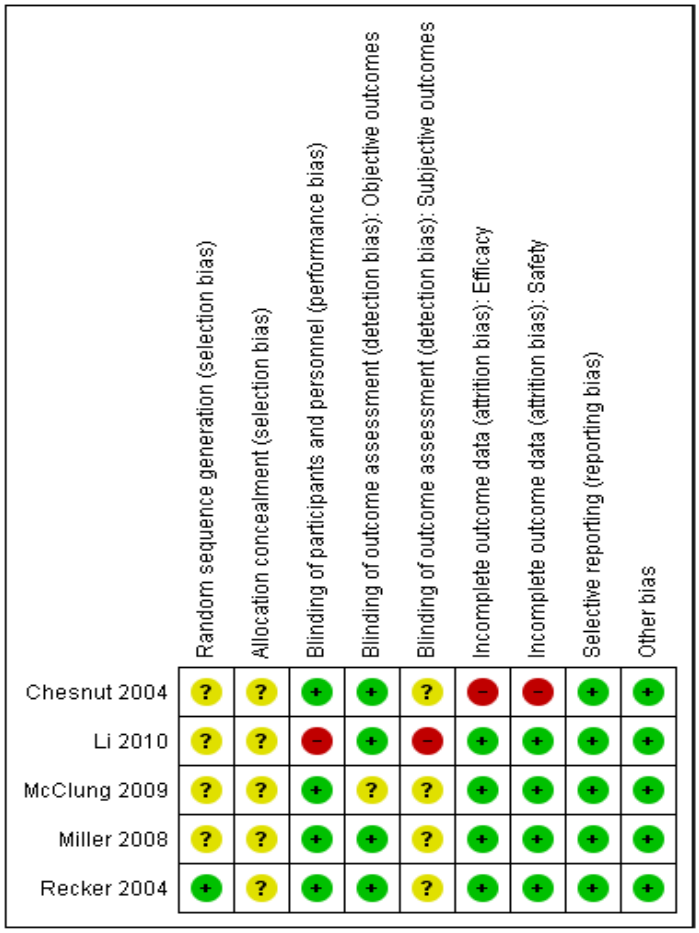


Figure 3. Risk of bias summary for included ibandronate studies[62,118-121] (Assessor's judgments about each risk of bias item for each included study).



3.3.4 Publication bias

As there was a small number of studies included in each analysis (3 in the ibandronate compared to placebo analysis and 2 in the ibandronate compared with alendronate analysis), it was not possible to create funnel plots to examine the possibility of publication bias. The low number of studies in each analysis does indicate that publication bias may indeed exist, but this could not be verified through the use of funnel plot analysis.

3.3.5 Main results of the meta-analysis

All results are shown as relative risk and 95% confidence intervals using random effects models. Results from the comparison ibandronate versus placebo are presented for the outcomes of vertebral, non-vertebral, and hip fractures, followed by total withdrawals and withdrawals due to adverse events. The same results are then presented for the comparison of ibandronate versus alendronate. Not all trials reported all outcomes, so the absence of outcomes does not indicate that no events occurred, only that data may not have been available for inclusion in the analysis (outcome data is reported in the study characteristic table in Appendix 3).

Forest plots show all included studies. By visual inspection of the forest plots, mild to moderate heterogeneity was seen for some outcomes (vertebral fractures and total withdrawals). Some outcomes such as hip fractures only had results from 1 arm of one study and therefore there was no statistical assessment of heterogeneity performed.

For the comparison of ibandronate versus placebo, the relative weight of the two large clinical trials was 100% for the outcome of vertebral fractures and therefore the results mainly reflect the results from these two trials.

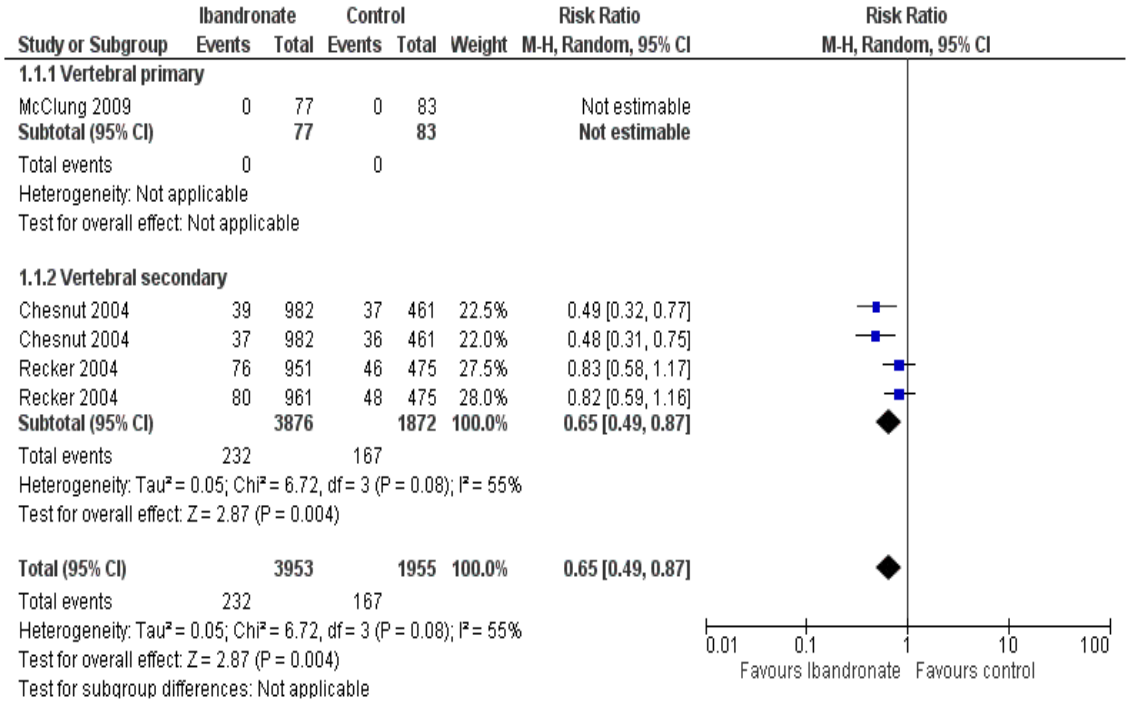
3.3.5.1 Ibandronate versus placebo

Two of the 3 studies in this analysis had 3 treatment arms using different dosage regimens for ibandronate, and a placebo arm. As a result these studies appear twice in the analyses to reflect each arm versus placebo. The results for the placebo arms were split (events and denominators) and applied to each active treatment arms as comparators, as recommended by the Cochrane Handbook[88].

A) Vertebral fractures

Incidence of patients sustaining at least one vertebral fracture was 5.9% in the ibandronate group and 8.5% in the placebo group. Overall, ibandronate treatment reduced the number of patients who sustained at least one vertebral fracture significantly (RR 0.65, 95% CI 0.49, 0.87). Heterogeneity was 56% by I^2 test statistics (moderate). Results are shown in Figure 4a.

Figure 4a. Forest plot ibandronate versus placebo: Vertebral fractures.

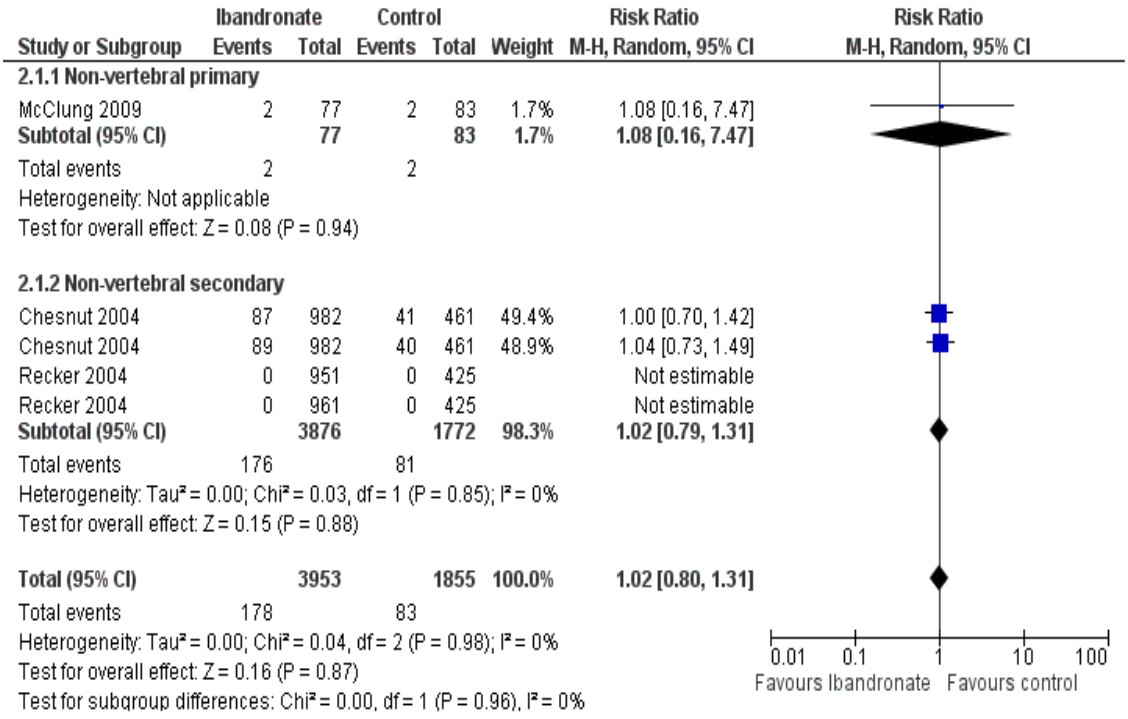


B) Non-vertebral fractures

Incidence of patients sustaining at least one non-vertebral fracture was 4.5% in the ibandronate group and 4.5% in the placebo group. Overall, ibandronate treatment did not reduce the number of patients who sustained a non-vertebral fracture significantly (RR 1.02, 95% CI 0.80, 1.31). Heterogeneity was 0% by I^2 test statistics (low), as most of the

results are from one study which accounted for 98.3% of the weight. Results are shown in Figure 4b.

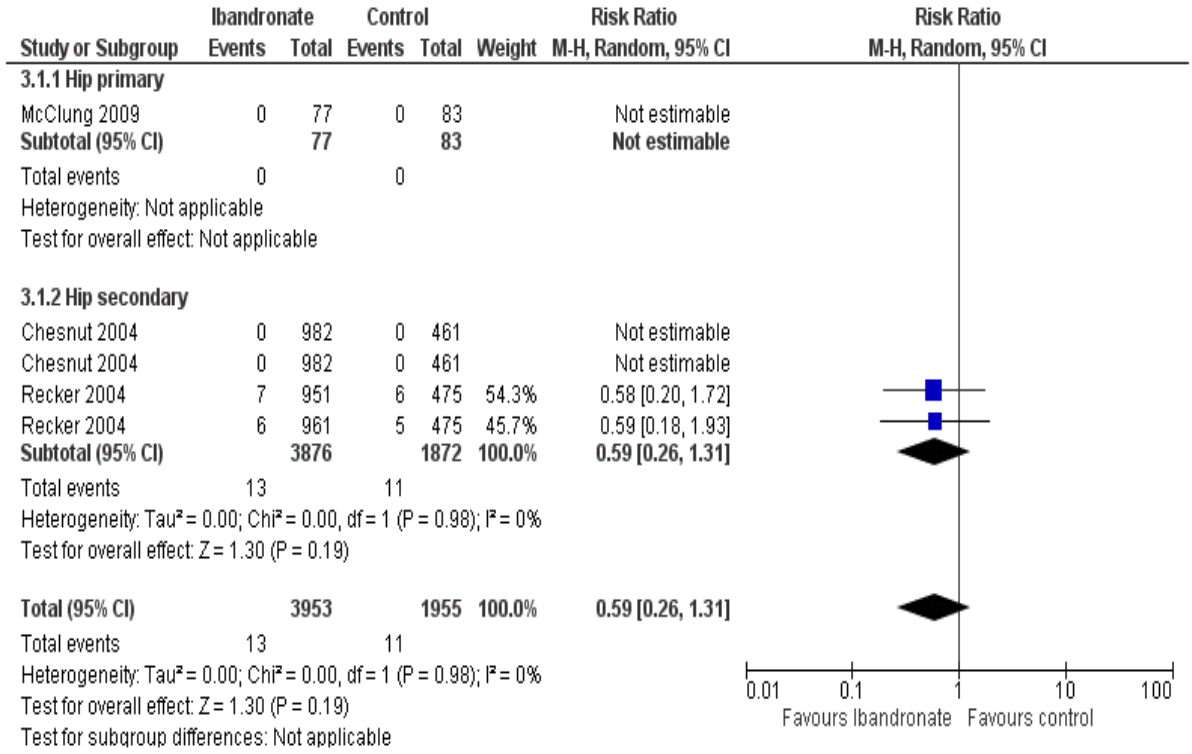
Figure 4b. Forest plot ibandronate versus placebo: Non-vertebral fractures.



C) Hip fractures

Incidence of patients sustaining a hip fracture was 0.33% in the ibandronate group and 0.59% in the placebo group. Overall, ibandronate treatment did not reduce the number of patients who sustained a hip fracture (RR 0.59, 95% CI 0.26, 1.31). Since all hip fractures occurred in one study heterogeneity was 0% by I^2 test statistics (low). Results are shown in Figure 4c.

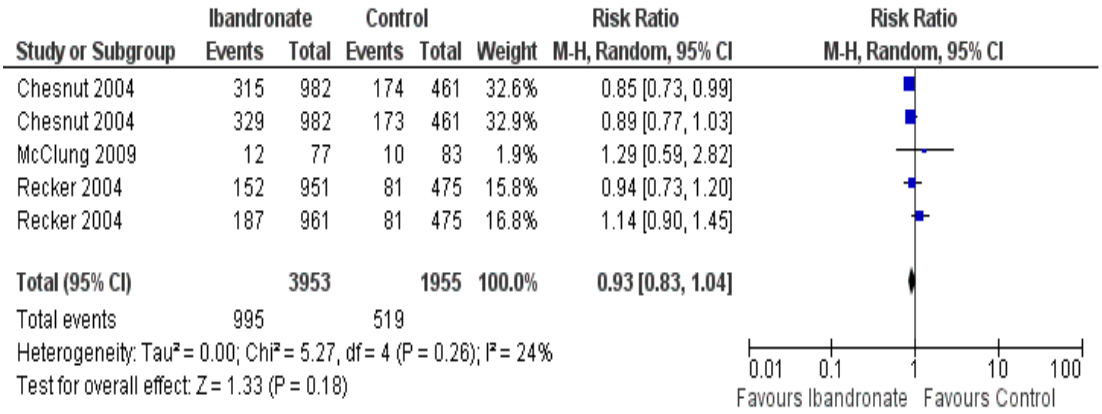
Figure 4c. Forest plot ibandronate versus placebo: Hip fractures.



D) Total withdrawals

Incidence of patients who withdrew for any reason was 25.2% in the ibandronate group and 26.5% in the placebo group. Overall, the total withdrawals was not different for ibandronate treatment versus placebo (RR 0.93, 95% CI 0.83, 1.04). Heterogeneity was 24% by I^2 test statistics (low). Results are shown in Figure 4d.

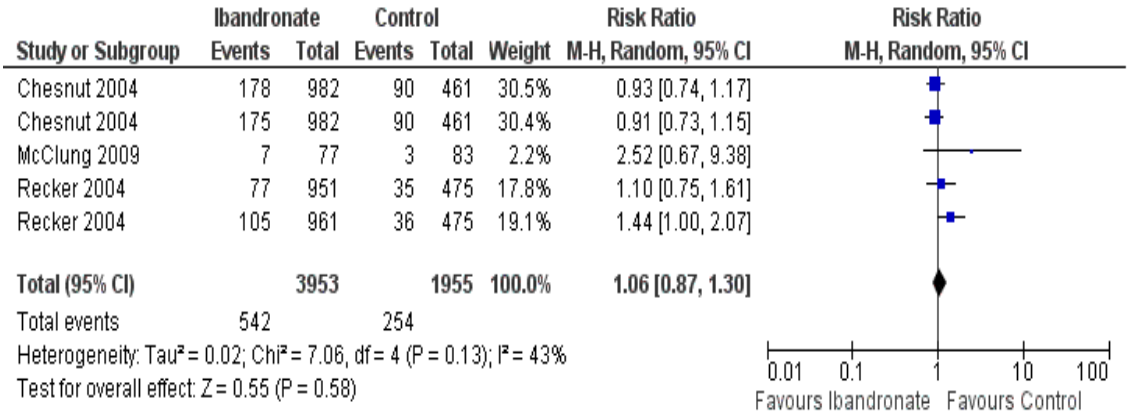
Figure 4d. Forest plot ibandronate versus placebo: Total withdrawals.



E) Adverse event withdrawals

Incidence of patients who withdrew due to adverse events was 13.7% in the ibandronate group and 13.0% in the placebo group. Overall, the withdrawals due to adverse events was not different for ibandronate treatment versus placebo (RR 1.06, 95% CI 0.87, 1.30). Heterogeneity was 43% by I^2 test statistics (low). Results are shown in Figure 4e.

Figure 4e. Forest plot ibandronate versus placebo: Adverse event withdrawals.

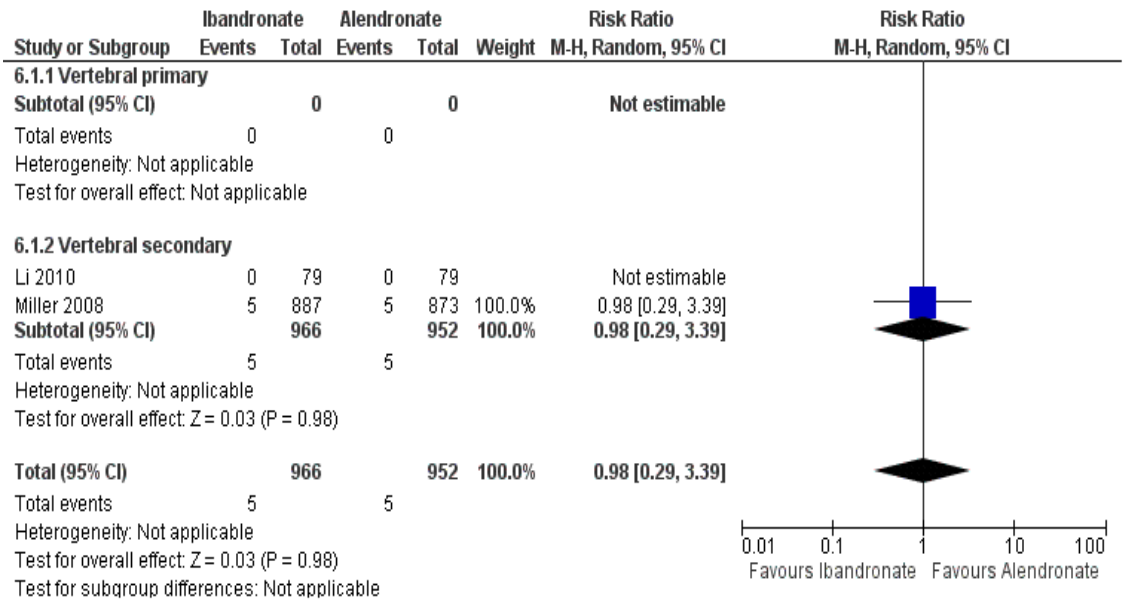


3.3.5.2 Ibandronate versus alendronate

A) Vertebral fractures

Vertebral fractures occurred in only one study in which the incidence of patients sustaining at least one vertebral fracture was 0.52% in the ibandronate group and 0.53% in the alendronate group. Overall, there was no difference in the two treatments (RR 0.98, 95% CI 0.29, 3.39). Heterogeneity testing did not apply as vertebral fractures occurred in only one study. Results are shown in Figure 5a.

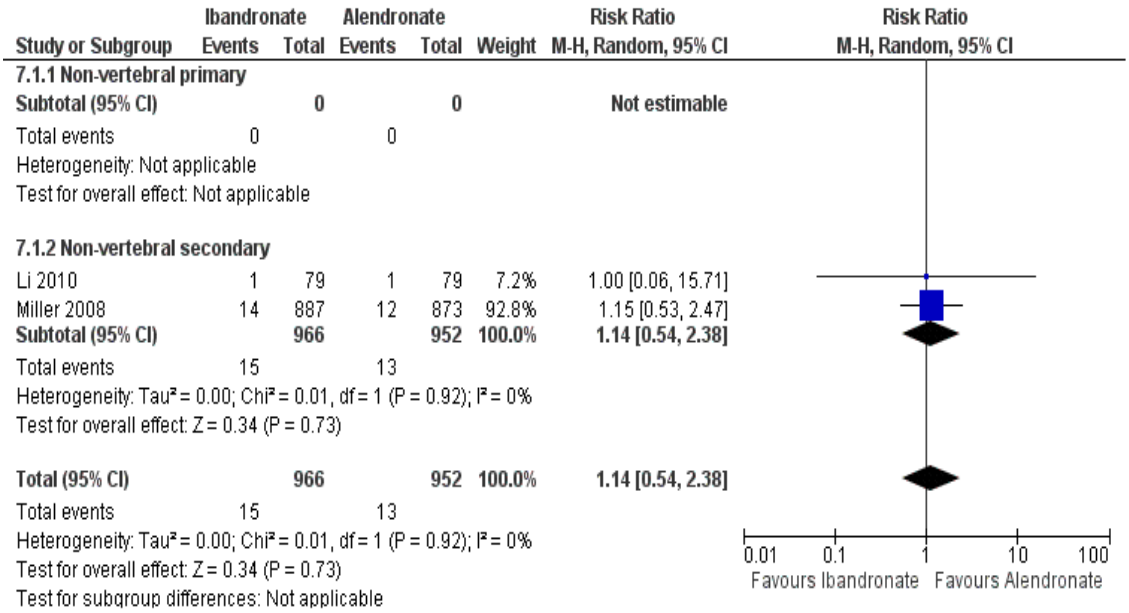
Figure 5a. Forest plot ibandronate versus alendronate: Vertebral fractures.



B) Non-vertebral fractures

The incidence of patients sustaining a non-vertebral fracture was 0.52% in the ibandronate group and 0.53% in the alendronate group. Overall, there was no difference in the two treatments (RR 1.14, 95% CI 0.54, 2.38). Heterogeneity was low (0%) as most of the weight was from one study (92.8%). Results are shown in Figure 5b.

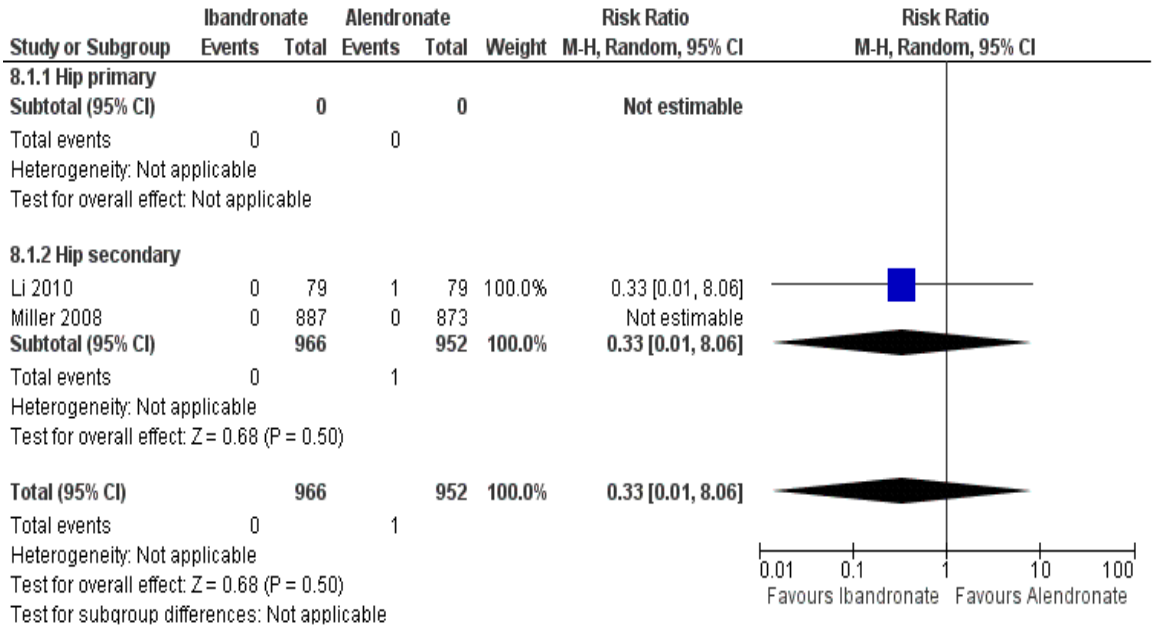
Figure 5b. Forest plot ibandronate versus alendronate: Non-vertebral fractures.



C) Hip fractures

Hip fractures occurred in only one study in which the incidence of patients sustaining at least one vertebral fracture was 0% in the ibandronate group and 1.3% in the alendronate group. Overall, there was no difference in the two treatments (RR 0.33, 95% CI 0.01, 8.06). Heterogeneity testing did not apply as hip fractures occurred in only one study. Results are shown in Figure 5c.

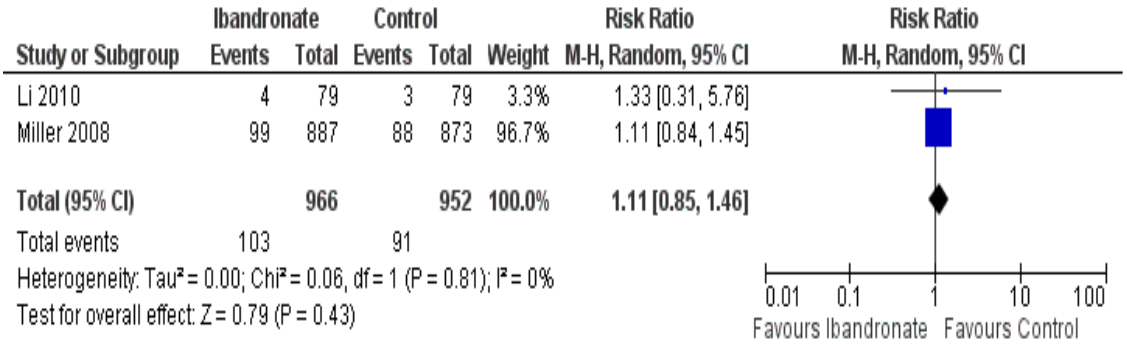
Figure 5c. Forest plot ibandronate versus alendronate: Hip fractures.



D) Total Withdrawals

Incidence of patients who withdrew for any reason was 10.7% in the ibandronate group and 9.6% in the alendronate group. Overall, the number of total withdrawals was not different in the two groups (RR 1.00, 95% CI 0.85, 1.46). Heterogeneity was low (0%) as most of the weight was from one study (96.7%). Results are shown in Figure 5d.

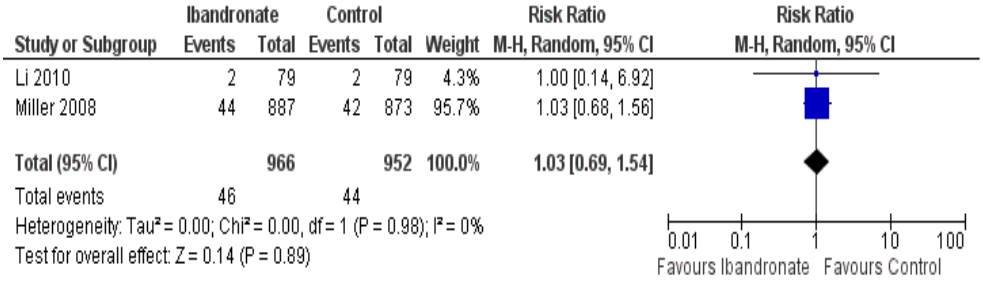
Figure 5d. Forest plot ibandronate versus alendronate: Total withdrawals.



E) Adverse event withdrawals

Incidence of patients who withdrew due to adverse events was 4.8% in the ibandronate group and 4.6% in the alendronate group. Overall, withdrawals due to adverse events was not different between the two treatments (RR 1.03, 95% CI 0.69, 1.54). Heterogeneity was low (0%) as most of the weight was from one study (96.7%). Results are shown in Figure 5e.

Figure 5e. Forest plot ibandronate versus alendronate: Adverse event withdrawals.



3.3.5.3 Subgroup analyses

Due to the small number of eligible studies, all the subgroup analyses that had been planned could not be performed. The Forest plots in the previous section do indicate which studies were primary and secondary prevention studies.

3.3.5.4 Sensitivity analyses

Sensitivity analyses were performed as planned for the fixed effects model and with the follow-up denominators for both the ibandronate versus placebo and ibandronate versus alendronate comparisons.

The results from the sensitivity analysis using the fixed effects model (with baseline denominators) for ibandronate versus placebo are presented in Table 7, with the results from the random effects model as comparators. The Forest plots are presented in Appendix 4. Results were consistent with the original analysis.

Table 7. Results of fixed effects model and random effects model analyses for ibandronate versus placebo.

Outcome	**Fixed effects RR (95% CI)**	**Random effects RR (95% CI)**
Vertebral Fractures	**0.68 (0.56, 0.82)**	**0.65 (0.49, 0.87)**
Non-Vertebral Fractures	1.02 (0.80, 1.31)	1.02 (0.80, 1.31)
Hip Fractures	0.59 (0.26, 1.31)	0.59 (0.26, 1.31)
Total withdrawals	0.93 (0.85, 1.02)	0.93 (0.83, 1.04)
Withdrawals due to AEs	1.03 (0.90,1.18)	1.06 (0.87, 1.30)

Note: Significant results are in bold font.

The results from the sensitivity analysis using the follow-up denominators for ibandronate versus placebo are presented in Table 8, with the results from the baseline denominators presented as comparators. The Forest plots are presented in Appendix 4. Results were consistent with the original analysis.

Table 8. Results of random effects model analyses using follow-up and baseline denominators for ibandronate versus placebo.

Outcome	**Follow-up denominators RR (95% CI)**	**Baseline denominators RR (95% CI)**
Vertebral Fractures	**0.66 (0.50, 0.88)**	**0.65 (0.49, 0.87)**
Non-Vertebral Fractures	1.04 (0.82, 1.33)	1.02 (0.80, 1.31)
Hip Fractures	0.59 (0.26, 1.31)	0.59 (0.26, 1.31)
Total withdrawals	0.93 (0.85, 1.03)	0.93 (0.83, 1.04)
Withdrawals due to AEs	1.07 (0.88, 1.29)	1.06 (0.87, 1.30)

Note: Significant results are in bold font.

The results from the sensitivity analysis using the fixed effects model (with baseline denominators) for ibandronate versus alendronate placebo are presented in Table 9, with the results from the random effects model as comparators. The Forest plots are presented in Appendix 4. Results were consistent with the original analysis.

Table 9. Results of fixed effects model and random effects model analyses for ibandronate versus alendronate.

Outcome	Risk Ratio, fixed effects (95% CI)	Risk Ratio, random effects (95% CI)
Vertebral Fractures	0.98 (0.29, 3.39)	0.98 (0.29, 3.39)
Non-Vertebral Fractures	1.14 (0.54, 2.38)	1.14 (0.54, 2.38)
Hip Fractures	0.33 (0.01, 8.06)	0.33 (0.01, 8.06)
Total withdrawals	1.11 (0.85, 1.46)	1.11 (0.85, 1.46)
Withdrawals due to AEs	1.03 (0.69, 1.54)	1.03 (0.69, 1.54)

The results from the sensitivity analysis using the follow-up denominators are presented in Table 10, with the results from the baseline denominators presented as comparators. The Forest plots are presented in Appendix 4. Results were consistent with the original analysis.

Table 10. Results of random effects model analyses for using follow-up and baseline denominators for ibandronate versus alendronate.

Outcome	Follow-up denominators RR (95% CI)	Baseline denominators RR (95% CI)
Vertebral Fractures	0.99 (0.29, 2.42)	0.98 (0.29, 3.39)
Non-Vertebral Fractures	1.15 (0.55, 2.40)	1.14 (0.54, 2.38)
Hip Fractures	0.34 (0.01, 8.01)	0.33 (0.01, 8.06)
Total withdrawals	1.13 (0.86, 1.47)	1.11 (0.85, 1.46)
Withdrawals due to AEs	1.04 (0.70, 1.56)	1.03 (0.69, 1.54)

3.4 Discussion

3.4.1 Summary of results

Overall, using the data available and a random effects model for meta-analysis, ibandronate was found to be effective compared with placebo for decreasing the risk of vertebral fractures. This was based mostly on secondary prevention studies and for ibandronate doses equivalent to an annual cumulative dose of 2-5.8 mg[118,119]. Because of the small number of studies that were available with fracture outcome data, it was not possible to perform subgroup analyses by dose or study duration.

Ibandronate was not found to be effective for the prevention of non-vertebral fractures or hip fractures. No data were available to assess efficacy with respect to wrist fractures outside of the context of non-vertebral fractures.

Total withdrawals were not found to be significantly different for ibandronate compared with placebo. The proportion of total withdrawals from studies was greater than 25% overall, which may have affected the final study results and magnitude of effects.

Withdrawals due to adverse events were not different for ibandronate compared with placebo. Overall, approximately 13% of subjects discontinued treatment due to adverse events. It should be noted that the rarer adverse events of concern (such as atypical fractures) are unlikely to be detected in clinical trials and that these adverse events are probably not represented.

No substantive differences in results were detected whether baseline or follow-up denominators were used. Similarly, the choice of either fixed effects or random effects models did not appreciably change the results.

When ibandronate and alendronate were compared using a random effects meta-analysis model, no differences were seen in the risk of vertebral, non-vertebral, and hip fractures.

In addition, there were no differences detected with respect to discontinuations overall and for those due to adverse events between ibandronate and alendronate.

3.4.2 Comparison to other reports

No other meta-analysis regarding ibandronate was identified through the systematic search or through examining the references of other articles. One report of a pooled analysis for ibandronate that examined its effectiveness in the prevention of non-vertebral fractures has been published[122]. This report included 9 studies (many of which did not meet the inclusion criteria for the present analysis) and pooled individual patient data; it found that higher annual cumulative doses of ibandronate (150 mg po monthly or 3 mg iv every 3 months) were effective at preventing non-vertebral fractures. The present study did not find that ibandronate was effective versus placebo or alendronate for the prevention of these fractures, but this may be due to the small amount of studies meeting the inclusion criteria and the differences in the methodologies of the two analyses.

3.4.3 Study limitations

Although only 5 studies were eligible for inclusion in the 2 meta-analyses, the results of this study are believed to be robust as the review was performed according to the accepted methodology for systematic reviews. The literature search was comprehensive and included multiple databases and also searched reference lists to locate additional publications. In addition, inclusion and exclusion criteria were explicitly specified and a conservative data analysis using a random effects model was performed. The initial search was updated to determine if newer publications were available, however none were identified.

However, there are limitations of this study with respect to the dose and route of administration of ibandronate, the quality of fracture assessment and classification, the lack of clarity regarding allocation concealment, assessment of adverse events, and the large numbers of withdrawals in the larger and longer-term studies.

Ibandronate was not used in the same doses and route of administration in the studies included that compared ibandronate and placebo, which may introduce heterogeneity and this needs to be considered when evaluating the results. By determining the annual cumulative doses of ibandronate used, based on its reported bioavailability, it is possible to know an approximate dose range used in the studies, which was calculated to be between 2 and 10.8 mg, which may have impacted the results of the primary studies. In addition, the bioavailability calculations are an approximation and bioavailability itself is affected by the composition and amount of food and water that is consumed. The duration of the studies that compared ibandronate and placebo were also different, but all were at least 1 year in duration, which has been used as a criteria in other meta-analysis of bisphosphonates, and this duration is considered to be sufficient to determine an effect regarding fracture prevention, although it may contribute to heterogeneity as well.

The quality of fracture assessment and classification is another potential source of heterogeneity, particularly in studies were the primary endpoint is not fracture, but BMD or another endpoint. In these studies fractures were reported as safety outcomes but may not have been detected; for example, vertebral fractures may be unsymptomatic and be undetected unless they are being actively assessed using radiographs at different intervals. For non-vertebral fractures there may be inconsistent reporting between trials with hip fractures being included or not in the total of non-vertebral fractures and as a result despite careful attention to fracture classification, there may be errors in classification.

Other methodological limitations that may increase the risk of bias in the included trials concern the lack of detail regarding the method of randomization and allocation concealment for most of the trials.

Although 2 of the included trials were 3 years in length, it is not possible to extrapolate about the long-term effects of ibandronate with respect to fracture prevention beyond the duration of the trials, and the duration of treatment with bisphosphonates continue to be a

matter of debate. The large number of total withdrawals in the longer term ibandronate trials was consistent with other long-term (3 years or more) trials of other bisphosphonates, indicating that over time a substantial proportion of patients decide, for a variety of reasons, that participation in the clinical trials is no longer appropriate for them. Although there was no difference seen between the treatment arms in the meta-analyses, treatment discontinuations may have affected the overall results.

The assessment of adverse events from clinical trials is limited as participants in these studies are carefully selected through strict inclusion and exclusion criteria and may be healthier than those who would normally be candidates for therapy. For example, as gastrointestinal ulcers are a known adverse event associated with bisphosphonate use, several studies excluded women with a previous history of gastrointestinal disorders, limiting the generalization of study findings. In addition, the reporting of adverse events in clinical trials has long been an issue of concern due to problems with under-reporting in scientific publications, classification of adverse events (serious or not), and determination of causality. In the trials included in these 2 analyses, it was unclear as to whether the assessors were blinded or not regarding the assessment of some adverse events. Clinical trials are not powered or designed to assess differences in uncommon or rare adverse events. Basic comparisons of the number withdrawals due to adverse events, or number of adverse events, between treatment arm is usually all that is reported in publications of clinical trials and therefore limits what can be assessed by a meta-analysis. As a result this study is limited by a lack of detail regarding specific adverse events and cannot assess long-term toxicity due to the limited study durations.

3.4.4 Conclusions

Ibandronate was shown to have a statistically significant benefit in the prevention of vertebral fractures when compared to placebo. Although it was not possible to conduct a subgroup analysis of primary and secondary prevention of such fractures due to the limited amount of data available, the majority of the evidence available is for the context of secondary prevention. It was not effective for the prevention of non-vertebral or hip

fractures. No differences were found for ibandronate compared to alendronate in the prevention of vertebral, non-vertebral or hip fractures.

No statistically significant difference was seen between treatment groups with respect to treatment discontinuations or discontinuations due to adverse events, suggesting that ibandronate was as equally tolerated by study participants as placebo and another bisphosphonate, alendronate.

4 SYSTEMATIC REVIEW AND META-ANALYSIS OF EFFICACY AND SAFETY OF ZOLEDRONIC ACID

4.1 Introduction

The following systematic review to identify studies investigating the use of zoledronic acid in the treatment of osteoporosis was performed according to the methods described in the Cochrane Handbook[88], and was similar to that performed for ibandronate and as discussed in Chapter 3. Any deviations from recommended methodology are reported.

4.2 Methods

4.2.1 Study inclusion criteria

The PICO criteria outlined below were used to determine if studies were to be included in the review.

- Types of studies

Only RCTs with a duration of at least one year were included.

- Types of participants

Studies that enrolled postmenopausal women were included. Both primary and secondary prevention trials were included to permit comparisons of outcomes by the severity of the condition of the participants. If a trial restricted the population to women whose bone density was at least 2 SD below the peak bone mass or to women who had already experienced a vertebral fracture, it was considered to be a secondary prevention trial (as these are indicators of more advanced bone loss). If the inclusion criteria were not provided or were not clear, a trial was considered to be a primary prevention study if the baseline characteristics indicated that the that the average T-score (and SD) was within 2 SD of the mean or the prevalence of vertebral fractures of the participants at baseline was less than 20%.

- Types of intervention and comparator

Studies that randomized patients to receive zoledronic acid at currently approved doses (or equivalents) and any route of administration or no treatment (including placebo or calcium plus vitamin D) were included. If the study used calcium and vitamin D controls, the same treatment had to be given concurrently in the zoledronic acid treatment group(s).

- Types of outcome measures

The efficacy outcome measures of interest were the incidence of fractures (number of women who sustained a fracture), and these were classified by vertebral, non-vertebral, hip and wrist fractures, where possible. Safety outcomes included the total number of withdrawals, number of withdrawals due to adverse events, and number of serious adverse events when available.

4.2.2 Search methods

A computerized search strategy was created with the assistance of an information scientist to incorporate both efficacy and safety outcomes. The following electronic databases where searched through December 12, 2011 using an OVID interface:

- CENTRAL, DARE, HTA Database and NHS EED, The Cochrane Library, 2011
- EMBASE, 1980 to 2011, week 49
- MEDLINE, 1948 to present and In-Process & Other Non-Indexed Citations
- Scopus
- WHO International Clinical Trials Registry Platform

No language limits were applied to the search. An example of a full search strategy is presented in Appendix 5.

In addition, the bibliographies of included articles, relevant systematic and non-systematic reviews were searched for additional references. The websites of the United

States Food and Drug Administration and the European Medicines Agency were searched for reviews and other documents relevant to zoledronic acid. These can be found at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=BONIVA
and
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000502/human_med_000677.jsp&mid=WC0b01ac058001d124.

4.2.3 Methods of the systematic review

4.2.3.1 Selection of studies

Article titles and abstracts were assessed against the PICO eligibility criteria in an un-blinded standardized manner by two assessors. If there were uncertainties regarding eligibility, these were resolved by discussion and consensus with the thesis supervisor. Any RCT that appeared to potentially meet the review criteria was obtained in full text format, after which the inclusion criteria were applied and a final decision was made concerning eligibility. There was no blinding of articles by study authors or research centres as this has not been demonstrated to appreciably improve the review process, but does increase workload[88].

In the event that there were multiple published reports or outcomes from one study, these publications were linked together and referred to by the included study. The primary study publication was the one used for data extraction. For this review there was no need to perform additional data extraction from the additional publications as they did not contain additional fracture information.

4.2.3.2 Data extraction and management

Data was extracted from each eligible publication using a standardized data abstraction form that was based on the Cochrane Consumer's and Communication Review Group's data extraction template[88].

Information that was extracted included: 1) study design; 2) inclusion criteria and major exclusion criteria; 3) characteristics of participants, including age, country, presence of vertebral fractures, and concomitant medication use; 4) type of intervention including study drug, duration of use, dose, frequency, and route of administration; 5) and outcomes assessed, including number of patients with vertebral, non-vertebral, hip and wrist fractures, total withdrawals, withdrawals due to adverse events, and serious adverse events.

4.2.3.2 Quality assessment

Each included study was assessed for quality using the Cochrane Collaboration's tool[88] for assessing risk of bias by two independent assessors, as described in section 3.2.3.2. Any uncertainties were discussed until consensus was reached between the assessors and confirmed with the supervisor.

4.2.3.4 Assessment of heterogeneity

Clinical heterogeneity was assessed by examining the clinical and methodological diversity of the studies. Meta-analyses were to only be performed if the participant characteristics, interventions, and outcome data of the included studies were assessed as being sufficiently homogeneous.

Statistical heterogeneity was to be assessed through examination of Forest plots to determine if there was an absence of overlap in the confidence intervals that would suggest heterogeneity[88], using the methodology described in section 3.2.3.4.

4.2.3.5 Data synthesis

Review Manager 5.1 software available from the Cochrane Collaboration (http://ims.cochrane.org/revman) was to be used for the statistical analyses, according to the guidelines of the Cochrane Handbook[88]. An approach using a random effects model was to be used as the primary analysis as was performed for ibandronate (see section 3.2.3.5).

4.2.3.6 Assessment of publication bias

The potential for publication bias was to be assessed by the creation of funnel plots for each outcome, as described in section 3.2.3.6.

4.2.3.7 Subgroup analyses

Subgroup analyses were planned similar to those that had been performed for the meta-analyses of alendronate, risedronate, and etidronate[11-13] and included primary versus secondary prevention trials, and treatment duration .

4.2.3.8 Sensitivity analyses

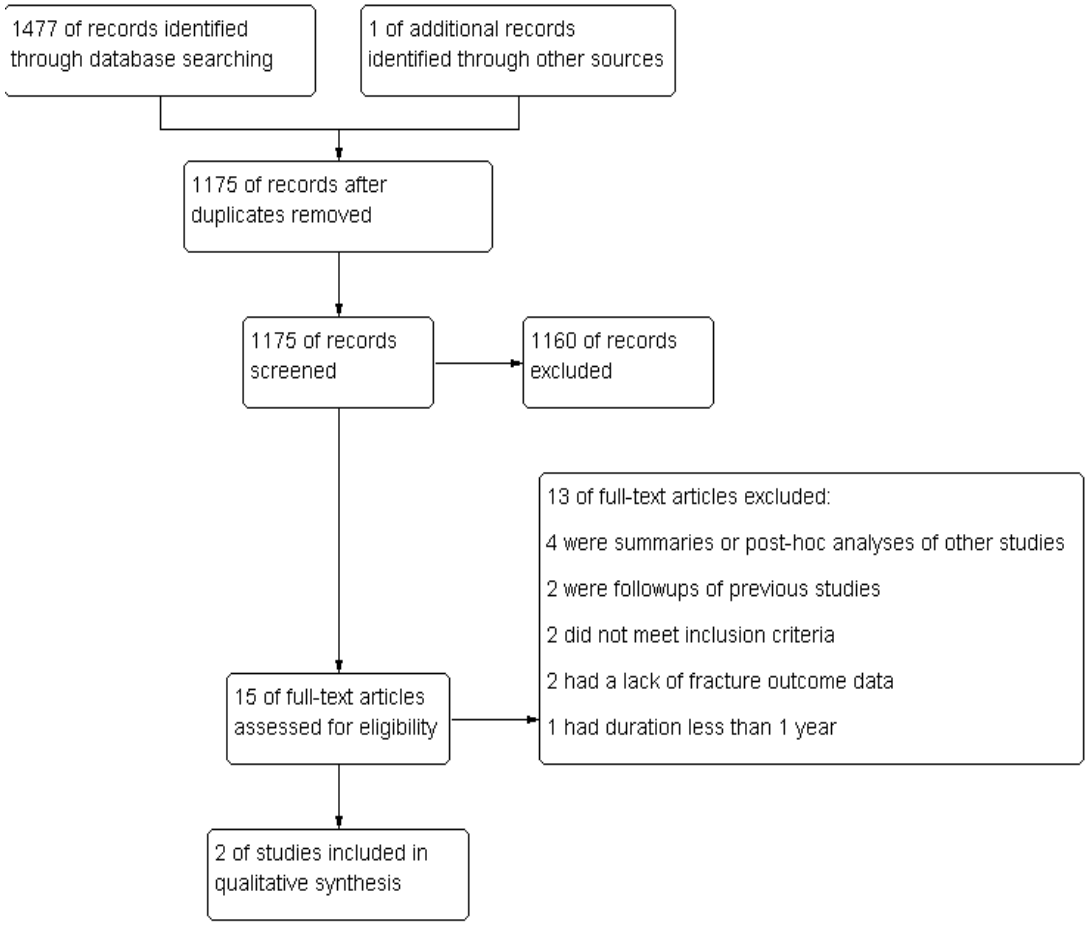
Sensitivity analyses were to be performed examining any difference in results using: 1) baseline denominators versus follow-up denominators; and 2) random effects versus fixed-effect models.

4.3 Results

4.3.1 Results of the search

The systematic search strategy identified 1175 studies of potential interest for the review after the removal of duplicate reports. After inspection of the title and/or abstract, 626 reports were excluded, and as a result the remaining 15 references were screened by reading the full text. Only 2 studies met the inclusion criteria. The review process is depicted in Figure 6.

Figure 6. Schematic of the review process for zoledronic acid.



Appendix 6 contains a list of excluded studies and the reasons for exclusion[123-135].

4.3.2 Included studies

In total, 2 trials met the original selection criteria for inclusion[136,137]. One was a primary fracture prevention trial of 1 year in duration and contributed 90 patients[136]; the other trial was a secondary prevention trial of 3 years in duration with a total of 7765 patients[137]. Both efficacy and safety outcomes were reported in all trials, but number of patients with new fractures was reported as an efficacy outcome in the secondary prevention trial[137] and as a safety outcome in the other trial[136].

All studies were reported in English. Main characteristics of the included studies are depicted in Appendix 7.

4.3.2.1 Characteristics of the patients

In both of the included trials[136,137] participants were postmenopausal women. In the secondary prevention trial, participants had and a BMD T-score less than -2.5 at the femoral neck with or without vertebral fractures, or a BMD T-score of less than 1.5 with at least 2 mild vertebral fractures or 1 moderate vertebral fracture. in at least one lumbar vertebra, and were therefore secondary prevention trials. In the primary prevention trial, participants had a lumbar spine or hip BMD T-score between -1 and 12. The mean age of women in the secondary trial was approximately 73 years, while it was lower in the primary study at approximately 65 years. Patients who had received previous treatment with bisphosphonates or those with disorders of bone metabolism were excluded from these studies.

4.3.2.2 Characteristics of the intervention and comparators

In the included trials that compared zoledronic acid and placebo, patients received either intravenous zoledronic acid at 5 mg iv annually or placebo iv annually. One trial[137] had two other zoledronic acid arms but both of these arms used doses less than the approved

dose of 5 mg iv annually, so did not meet the inclusion criteria and these data were not extracted. All patients received calcium and vitamin D supplements.

4.3.2.3 Characteristics of the outcomes

The larger of the two trials[136] had a primary efficacy endpoint of the number of new vertebral and hip fractures. Secondary endpoints were non-vertebral and clinical fractures. Total withdrawals and withdrawals due to adverse events were reported. The smaller trial[137] had markers of bone turnover as the primary endpoint, but reported non-vertebral fractures as adverse events and total withdrawals. Neither trial reported wrist fractures as an endpoint.

4.3.3 Quality assessment

The assessment of study quality yielded a low risk of bias in most domains. Allocation concealment was not addressed in the larger study[136] and this resulted in an "unclear" assessment in this domain.

The results of the risk of bias assessment using the tools provided in RevMan are shown in Figures 7 and 8.

Figure 7. Risk of bias graph for included zoledronic acid studies[136,137] (Assessor's judgments about each risk of bias item presented as percentages across all included studies).

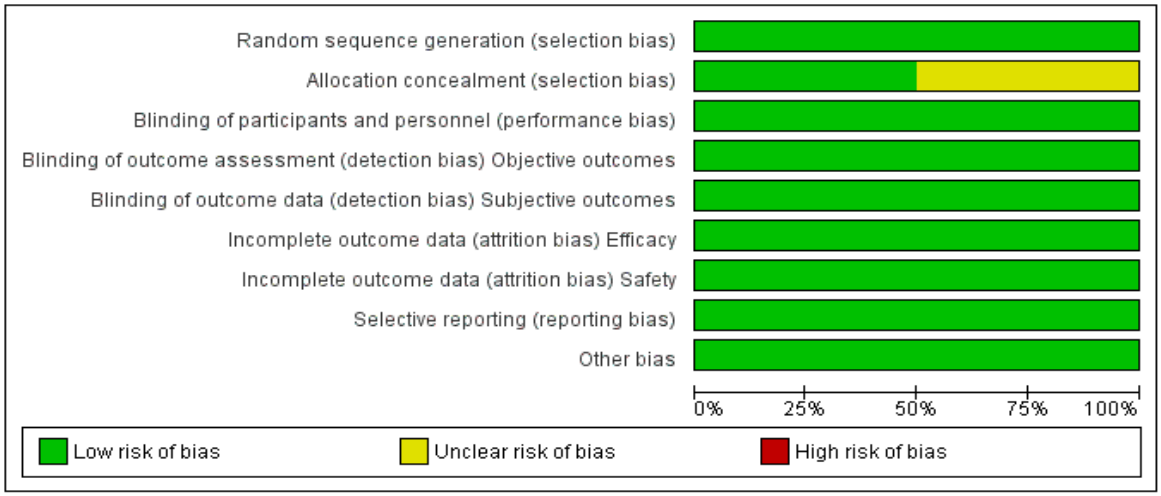


Figure 8. Risk of bias summary for included zoledronic acid studies[136,137] (Assessor's judgments about each risk of bias item for each included study).

4.3.4 Publication bias

As there were only two studies identified by the systematic review, it was not possible to create funnel plots to examine the possibility of publication bias. The low number of studies does indicate that publication bias may indeed exist, but this could not be verified through the use of funnel plot analysis.

4.3.5 Main results from identified studies

The results from the two studies identified in the systematic review are shown in Table 11.

Table 11. Outcomes identified in the systematic review for zolendronic acid.

Trial and participants	Vertebral Fractures	Non-vertebral fractures	Hip Fractures	Wrist Fractures	Total Withdrawals	Adverse Event Withdrawals
Black 2007[136] Placebo: 3876 Zol[a]: 3889	Placebo: 310 Zol: 92 RR (95% CI)[c]: 0.30 (0.24-0.38)	Placebo: 388 Zol: 292 HR (95% CI)[d]: 0.75 (0.64-0.87)	Placebo: 88 Zol: 52 HR (95% CI): 0.59 (0.42-0.83)	N/A[b]	Placebo: 1158 Zol: 1126	Placebo: 182 Zol: 210
Grey 2012[137] Placebo: 45 Zol: 45	Placebo: 0 Zol: 0	Placebo: 2 Zol: 4	Placebo: 0 Zol: 0	N/A	Placebo: 1 Zol: 1	N/A

[a]Zol, Zoledronic acid. [b]N/A, not applicable. [c]RR (95% CI), Relative Risk (95% Confidence Interval). [d]RR (95% CI), Hazard Ratio (95% Confidence Interval).

Overall, the data available indicate that zoledronic acid is effective for the prevention of vertebral and hip fractures in postmenopausal women with osteoporosis. This is primarily based on the results of one trial[136], which had a participant population of 7765 and was conducted over 3 years, using a dose of 5 mg iv annually. Because of the small number of studies that were identified with the systematic review, it was not possible to perform a meta-analysis or the planned subgroup analyses.

This study also found that zoledronic acid was effective in the prevention of hip (HR 0.59; 95% CI 0.42, 0.83) and non-vertebral fractures (HR 0.75; 95% CI 0.64, 0.87). No data were available to assess efficacy with respect to wrist fractures outside of the context of non-vertebral fractures.

Total withdrawals and adverse event withdrawals were reported for this trial, but the study was not designed to detect a difference between zoledronic acid and placebo. The percentage of patients who withdrew from the zoledronic acid arm was 28.9% and from the placebo arm was 29.9%. The percentage of patients who withdrew due to adverse events was 5.4% in the zoledronic acid arm and 4.7% in the placebo arm.

The smaller study[137] that met the inclusion criteria reported no vertebral fractures in either relevant arm and only non-vertebral fractures were found. One patient withdrew from each arm (2.2%) in this study, but adverse event withdrawals were not reported.

4.4 Discussion

4.4.1 Summary of results

Overall, the data available indicate that zoledronic acid is effective for the prevention of vertebral and hip fractures in postmenopausal women with osteoporosis. This is primarily based on the results of one large trial. This study also found that zoledronic acid was effective in the prevention of hip and non-vertebral fractures. Total withdrawals and adverse event withdrawals were not different for zoledronic acid and placebo for either study that was found through the systematic review.

4.4.2 Comparison to other reports

No previous meta-analyses comparing the efficacy and safety of zoledronic acid to placebo were identified during the systematic review or other literature searches, and

therefore the results of this study cannot be compared to other studies. A probable reason is the lack of other RCTs with zoledronic acid; it received market authorization[76] on the basis of the one large trial and was the primary study that has been performed with this product.

4.4.2 Study limitations

Although only 2 studies were identified from the systematic review, these results are believed to be robust as the review was performed according to the accepted methodology for systematic reviews. The literature search was comprehensive and included multiple databases and also searched reference lists to locate additional publications. Information on the basis of marketing approval for zoledronic acid indicate that the product was approved for postmenopausal osteoporosis on the basis of the one pivotal trial which was identified in the present review. Studies that were excluded from inclusion in this review were primarily due to a lack of fracture outcome data, or because they were post-hoc analyses or subset analyses of the trial that did meet the inclusion criteria.

The second study that met the criteria for inclusion in this review was a small study that investigated the effects of different doses of zoledronic acid, including 5 mg, versus placebo. The primary endpoint was BMD, however fractures were reported as adverse events. Because of the small numbers of participants in this study there were few fracture events.

As discussed Chapter 3, some vertebral fractures may have been unsymptomatic and undetected in the smaller trial. For the larger trial this was less of a concern as vertebral fracture was a primary endpoint and participants were being actively assessed using radiographs at different intervals.

Overall both trials were assessed as having low risk of bias, however it was unclear how allocation concealment was addressed in one trial.

4.4.3 Conclusions

Based on the results of one large, pivotal trial, zoledronic acid is effective versus placebo for the prevention of vertebral, non-vertebral and hip fractures. No meta-analyses have been performed for the effectiveness of zoledronic acid versus placebo, however, zoledronic acid has been included in several network meta-analyses comparing osteoporosis treatments[69-71], and these are discussed further in Chapter 5.

5 NETWORK META-ANALYSIS

5.1 Introduction

Network meta-analysis is a type of indirect treatment comparison, the first of which was described by Bucher et al[67]. In this first method of adjusted indirect comparisons, two competing interventions can be adjusted with respect to their direct comparisons with a common control. This technique allows the researcher to maintain some of the advantages of randomized controlled trials in the analysis.

Mixed treatment comparisons were introduced later[68], and this technique permits the analysis of the results of several interventions to be compared to each other; this is known as a "network" of trials. It allows all the available evidence from RCTs to be incorporated into the analysis, using both direct and indirect evidence to compare interventions.

Network meta-analysis is being used more frequently to compare interventions that are unlikely to be the subject of direct head-to-head clinical trials and as such maximize the information that is available in a therapeutic area. As statistical software packages become more user-friendly and accessible, these techniques will be used more in the future. Both frequentist and Bayesian approaches are available for conducting network analysis and often both techniques are used and results compared.

5.2 Methods

5.2.1 Selection of studies

Studies that compared alendronate, risedronate, etidronate, ibandronate, and zoledronic acid to each other or placebo were identified through previously conducted systematic reviews and meta-analyses performed by Wells et al [11-13], and as previously described in Chapters 3 and 4. The original literature searches that had been previously performed for alendronate, risedronate and etidronate were repeated to determine if there were newly

identified studies that would meet the inclusion criteria for this study. The inclusion criteria for the studies for this network analysis were based on the meta-analyses and are as described in Chapters 3 and 4. Briefly, participants were post-menopausal women that had been diagnosed with osteoporosis on the basis of BMD and history of vertebral fracture.

Only studies that included doses that were the equivalent of authorized doses were included in this analysis to make the study more useful and reflect what is currently used as therapy. This was an issue for ibandronate, as different doses and routes of administration were used for this therapy, and for zoledronic acid. Only two "head-to-head" studies of bisphosphonates were identified that compared ibandronate and alendronate (described in Chapter 3).

The outcomes of interest were as previously described: vertebral, non-vertebral, hip and wrist fractures, and total withdrawals and withdrawals due to adverse events. The unit of analysis was number of fracture events (over the entire study period), as this was most commonly reported outcome in the literature, and not all studies reported the number of patients with fractures.

5.2.2 Mixed treatment comparison using Bayesian methods

Mixed treatment comparison (MTC) models were performed using Bayesian methods[68]. The software package WinBUGS (version 1.4.3) was used, which is the Windows© version of BUGS (Bayesian Inference Using Gibbs Sampling). This software was created at the MRC Biostatistical Unit in Cambridge, U.K., and can be now downloaded free of charge (www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml). The software uses a Monte Carlo chain simulation to construct the results. In this study 40 000 iterations were performed for each analysis.

Several programming codes can be used to perform the MTC analyses, including: 1) fixed effect models for 2-arm trials, 2) simple random effect models for 2-arm trials

(where no correlations induced by multi-arm trials has to be considered), 3) random effects models for 3-arm trials, and 4) random or fixed effects models for multi-arm trials. Sample codes as well as background introductory material may be found at: https://www.bris.ac.uk/cobm/research/mpes/mtc.html.

Random effects and fixed effects models were used for this analysis. The random effects model is a more conservative approach and allows that the true effect size may vary from study to study. The fixed effects model assumes that there is a single true effect value that is common to all studies. Both were performed and the results compared to each other, with the intention that the random effects analysis would be the primary analysis and the fixed effects model would serve as a sensitivity analysis.

For each comparison informative priors were used based on a review of meta-analyses that investigated between-study heterogeneity[138]. In some instances priors had to be modified to allow the model to converge, especially for those outcomes with fewer studies (such as wrist fractures).

Priors were then combined with the extracted trial data to derive posterior distributions for all unknown model parameters. Results are reported as odds ratios (OR) with 95% credible intervals (95% CrI); credible intervals are considered to be the Bayesian equivalent of a classical confidence interval.

Examples of the final codes, details on modifications of informative and vague priors, and convergence assessment are shown in Appendix 8.

In accordance with recommendations on conducting network meta-analyses[139], inconsistency was evaluated through the use of a random effects inconsistency model applied in WinBUGS. The code used, along with the results of the analyses, are shown in Appendix 9.

Network diagrams were created using NodeXL, a free, open-source template for Microsoft® Excel® that can be used to create network graphs. It can be downloaded from: http://nodexl.codeplex.com/.

The resultant odds ratios and the placebo group event rates were used to calculate the number needed to benefit or harm using the online tool available from: http://www.nntonline.net/visualrx/.

5.2.3 Network analysis using frequentist methods

Network analysis was performed using the PROC GLIMMIX procedure of SAS© version 9.3 (available from: http://www.sas.com) , which allows the user to specify a generalized linear mixed model (GLMM) and to perform confirmatory inference. It fits statistical models to data with correlations or nonconstant variability and where the response is not necessarily normally distributed. GLMMs have been used for analysis such as estimating trends in disease rates and modeling CD4 counts in a clinical trial over time.

GLMMs assume normal (Gaussian) random effects. Conditional on these random effects, data can have any distribution in the exponential family. The exponential family comprises many of the elementary discrete and continuous distributions. The binary, binomial, Poisson, and negative binomial distributions are some of the discrete members of this family while the normal, beta, gamma, and chi-square distributions are representatives of continuous distributions.

A binomial model was used in this thesis for each outcome to estimate odds ratios and 95% confidence intervals (95% CI). Both random and fixed effects models were used. The models are shown in Appendix 10.

5.2.4 Subgroup analyses

Similar to the analyses performed in Chapter 3, the planned subgroup analyses were primary versus secondary prevention trials and treatment duration (studies greater than or equal to 3 years and those less than 3 years).

5.2.5 Sensitivity analyses

As per the analyses performed in Chapter 3, the planned sensitivity analyses were baseline denominators versus follow-up denominators and random effects versus fixed-effect models.

5.3 Results

5.3.1 Included Studies

The number of included studies for each outcome varied as not every outcome was reported for every study. For example, the outcome with the greatest number of studies was total withdrawals, while wrist fractures were infrequently reported. Appendix 11 shows the trials that were included for each outcome analysis[62, 108,118,120,121, 136, 140-161], the characteristics of additional studies that were included after repeating the searches[159,161-163,168,169], and the studies from the original meta-analyses that were excluded as they did not meet this study's inclusion criteria[170,-175] .The key characteristics for trials that had already been included in the previous meta-analyses can be found in those publications[11-13], while the study characteristics for ibandronate and zoledronic acid can be found in Appendices 3 and 7.

5.3.2 Mixed treatment comparisons – Bayesian analysis

The following tables and figures show the results for the Bayesian analytical approach generated using WinBUGS.

For each outcome (vertebral, non-vertebral, hip and wrist fractures; total and adverse event withdrawals) a network diagram is presented. The size of the treatment spheres represents the number of patients exposed to that treatment in all of the studies; the lines show direct comparisons between treatments (most often versus placebo); and the width of the lines indicates the number of RCTs. Indirect comparisons are not shown as this would create very complicated diagrams. Each table shows the comparison of each treatment to each other and placebo (odds ratios, 95% credible intervals) for each outcome. Bolded values indicate significant results.

Finally, the number needed to treat (for benefit or harm) for each bisphosphonate versus placebo for each outcome is presented.

Figure 9a. Network diagram for vertebral fractures.

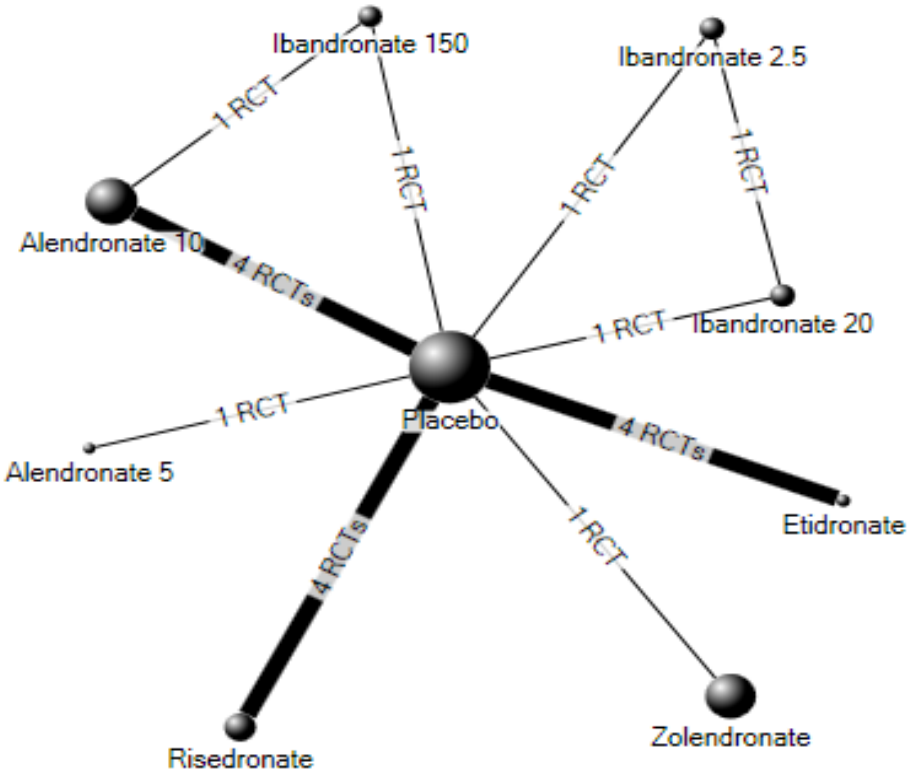


Table 12a. Bayesian MTC for bisphosphonates: Vertebral fractures. [Odds Ratio (95% Credible Interval)].

Treatment	Placebo	ALN^{5}	ALN^{10}	ETI	IBA^{150}	IBA$^{2.5}$	IBA^{20}	RIS	ZOL
Placebo	--	--	--	--	--	--	--	--	--
ALE^{5}	0.62 (0.15, 2.37)	--	--	--	--	--	--	--	--
ALE^{10}	**0.53 (0.40, 0.71)**	0.85 (0.22, 3.58)	--	--	--	--	--	--	--
ETI	**0.47 (0.23, 0.94)**	0.85 (0.22, 3.58)	0.89 (0.40, 1.87)	--	--	--	--	--	--
IBA^{150}	0.51 (0.13, 1.96)	0.82 (0.12, 5.60)	0.97 (0.26, 3.57)	1.08 (0.24, 4.93)	--	--	--	--	--
IBA$^{2.5}$	**0.49 (0.30, 0.79)**	0.77 (0.19, 3.45)	0.92 (0.52, 1.62)	1.04 (0.44, 2.44)	0.95 (0.23, 4.06)	--	--	--	--
IBA^{20}	**0.51 (0.32, 0.83)**	0.82 (0.20, 3.67)	0.97 (0.55, 1.69)	1.08 (0.47, 2.60)	1.00 (0.29, 4.60)	1.05 (0.62, 1.80)	--	--	--
RIS	**0.59 (0.45, 0.78)**	0.95 (0.25, 3.96)	1.12 (0.60, 2.71)	1.25 (0.60, 2.71)	1.15 (0.29, 4.60)	1.21 (0.69, 2.15)	1.15 (0.66, 2.03)	--	--
ZOL	**0.28 (0.20, 0.40)**	0.45 (0.11, 1.92)	**0.53 (0.33, 0.82)**	0.59 (0.27, 1.34)	0.54 (0.13, 2.23)	0.57 (0.31, 1.05)	**0.54 (0.30, 0.99)**	**0.47 (0.30, 0.74)**	--

Note: ALE^{5}, alendronate 5 mg/day po (35 mg/week); ALE^{10}, alendronate 10 mg/day po (70 mg/week); ETI, 400 mg/month po; IBA^{150}, ibandronate 150 mg/month po; IBA$^{2.5}$, 2.5 mg/day po; IBA^{20}, 20 mg/day po intermittently; RIS, risedronate 150 mg/month po; ZOL, zoledronic acid 5 mg/year iv. Statistically significant results are in bold font.

Seventeen studies[62,118,136,140-153] had vertebral fracture outcome data that could be assessed and were included in the Bayesian MTC analysis (total participants 22859). There were two trials that included comparisons between bisphosphonates: one trial[62] compared alendronate 10 mg/day po to ibandronate 150 mg/month po and placebo, and the other trial compared ibandronate 2.5 mg/day po to ibandronate 20 mg intermittently po and placebo[118]. All other studies compared various bisphosphonates to placebo. Figure 9a shows the network diagram for vertebral fractures.

The analysis showed that all the treatments, with the exception of alendronate 5 mg/day po and ibandronate 150 mg/month po, were effective at preventing vertebral fractures (Table 12a). The ORs (95% CrI) ranged from a high of 0.59 (0.45, 0.78) for risedronate 150 mg/month po to a low of 0.28 (90.20, 0.40) for zoledronic acid 5 mg/year iv, indicating that zoledronic acid is the most effective bisphosphonate for vertebral fracture prevention.

The comparisons of each bisphosphonate to each other revealed that zoledronic acid was significantly better at preventing vertebral fractures than alendronate 10 mg/day po (OR 0.53; 95% CrI 0.33, 0.82), ibandronate 20 mg intermittently po (OR 0.54; 95% CrI 0.30, 0.99), and risedronate 150 mg/month po (OR 0.47; 95% CrI 0.30, 0.74).

Figure 9b. Network diagram for non-vertebral fractures.

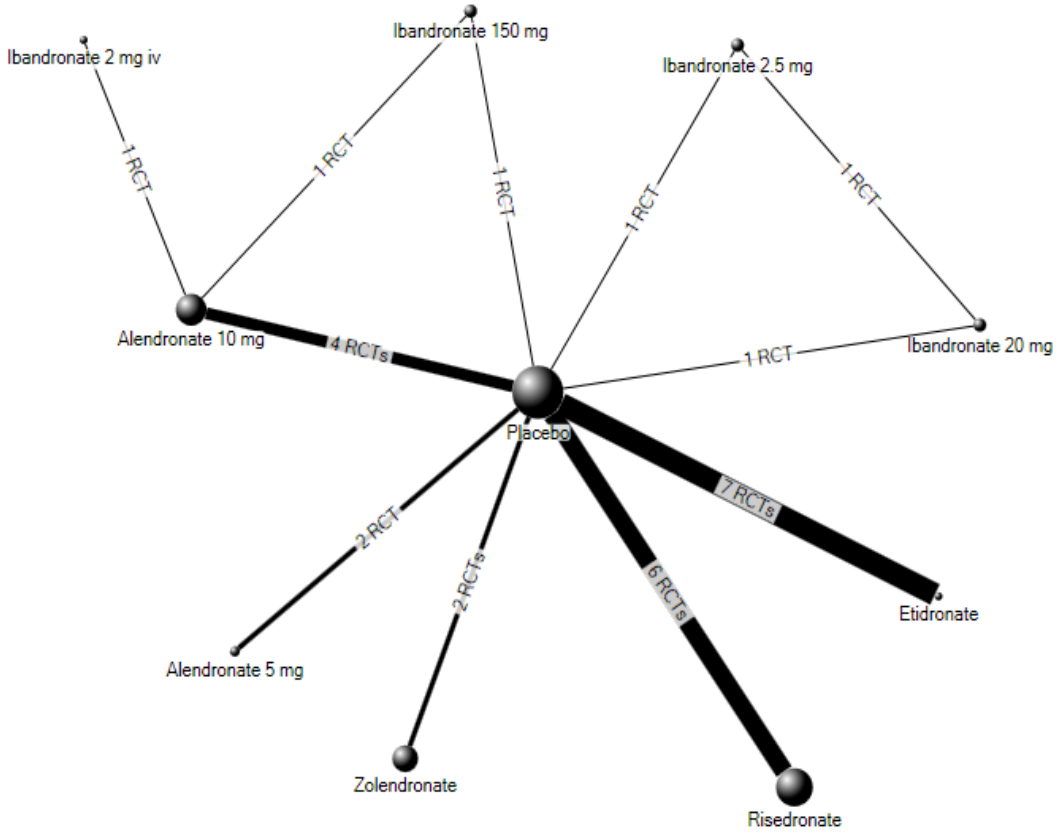


Table 12b. Bayesian MTC for bisphosphonates: Non-vertebral fractures. [Odds Ratio (95% Credible Interval)].

Treatment	Placebo	ALN^{5}	ALN^{10}	ETI	IBA^{2}	IBA^{150}	IBA$^{2.5}$	IBA^{20}	RIS	ZOL
Placebo	--	--	--	--	--	--	--	--	--	--
ALE^{5}	1.02 (0.58, 1.78)	--	--	--	--	--	--	--	--	--
ALE^{10}	**0.78 (0.59, 0.95)**	1.32 (0.72, 2.44)	--	--	--	--	--	--	--	--
ETI	0.67 (0.40, 1.10)	0.66 (0.31,1.41)	0.87 (0.50, 1.51)	--	--	--	--	--	--	--
IBA^{2}	0.82 (0.013, 46.85)	0.81 (0.012, 48.90)	1.07 (0.017, 59.45)	1.25 (0.021, 68.73)	--	--	--	--	--	--
IBA^{150}	0.91 (0.41, 2.08)	0.94 (0.34, 2.45)	1.18 (0.56, 2.63)	1.37 (0.54, 3.53)	1.10 (0.019, 75.84)	--	--	--	--	--
IBA$^{2.5}$	1.11 (0.72, 1.69)	1.09 (0.54, 2.22)	1.43 (0.91, 2.39)	1.66 (0.86, 3.23)	1.33 (0.023, 84.69)	1.21 (0.49, 3.00)	--	--	--	--
IBA^{20}	1.08 (0.70, 1.65)	1.06 (0.52, 2.17)	1.39 (0.88, 2.33)	1.62 (0.84, 3.14)	1.31 (0.023, 82.76)	1.18 (0.47, 2.92)	1.03 (0.67, 1.57)	--	--	--
RIS	**0.75 (0.57, 0.91)**	0.73 (0.39, 1.33)	0.96 (0.70, 1.33)	1.11 (0.63, 1.920	0.90 (0.016, 55.8)	0.81 (0.35, 1.82)	0.67 (0.40, 1.06)	0.69 (0.41, 1.10)	--	--
ZOL	0.73 (0.53, 1.02)	0.72 (0.38, 1.40)	0.94 (0.66, 1.48)	1.10 (0.61, 2.02)	0.89 (0.015, 54.92)	0.80 (0.33, 1.91)	0.66 (0.39, 1.14)	0.68 (0.40, 1.1.8)	0.98 (0.68, 1.53)	--

Note: ALE^{5}, alendronate 5 mg/day po (35 mg/week); ALE^{10}, alendronate 10 mg/day po (70 mg/week); ETI, 400 mg/month po; IBA^{2}, ibandronate 2 mg/every 3 months iv; IBA^{150}, ibandronate 150 mg/month po; IBA$^{2.5}$, 2.5 mg/day po; IBA^{20}, 20 mg/day po intermittently; RIS, risedronate 150 mg/month po; ZOL, zoledronic acid 5 mg/year iv. Statistically significant results are in bold font.

Twenty-seven studies[62,108,118,120,121,136,137,140-142,144-148,150-161] had non-vertebral fracture outcome data that could be assessed and were included in the analysis (total participants 36 408). There were three trials that included comparisons between bisphosphonates: the first trial compared alendronate 10 mg/day po to ibandronate 2 mg every 3 months iv[121], the second trial[52] compared alendronate 10 mg/day po to ibandronate 150 mg/month po and placebo, and the third trial compared ibandronate 2.5 mg/day po to ibandronate 20 mg intermittently po and placebo[118]. All other studies compared various bisphosphonates to placebo. Figure 9b shows the network diagram for non-vertebral fractures.

The analysis showed that only alendronate 10 mg/day po (OR 0.78; 95% CrI 0.59, 0.95) and risedronate 150 mg/month po (OR 0.75; 95% CrI 0.57, 0.91) were effective at preventing non-vertebral fractures compared to placebo (Table 12b). Of note the results for zoledronic acid almost reached significance compared to placebo (OR 0.73; 95% CrI 0.53, 1.02).The comparisons of each bisphosphonate to each other did not reveal that any bisphosphonate was more effective at preventing non-vertebral fractures.

There was only one study that included ibandronate 2 mg every 3 months iv and the results of the comparisons with this product had wide credibility intervals for every comparison, for example compared with placebo the OR was 0.82 and the 95% CrI was 0.013, 46.85. This is most likely due to the low numbers of events (1) and participants (79) in this arm of the study compared to the other products.

Figure 9c. Network diagram for hip fractures.

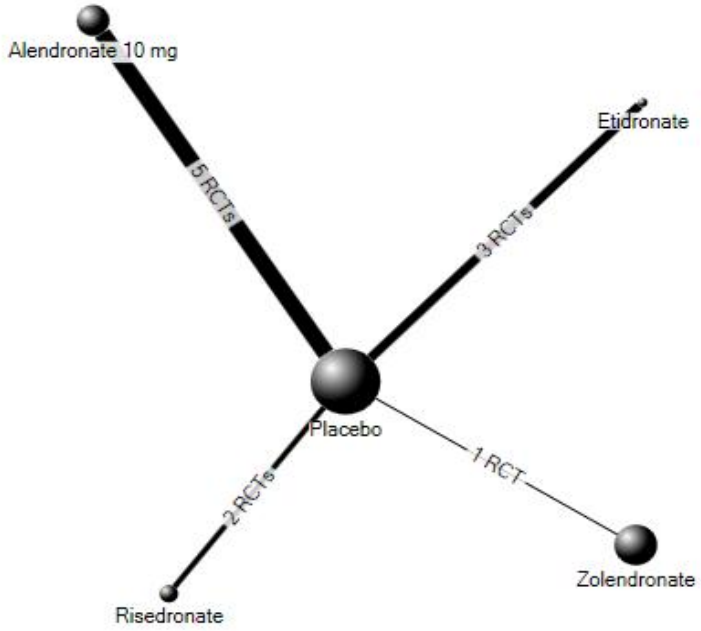


Table 12c. Bayesian MTC for bisphosphonates: Hip fractures. [Odds Ratio (95% Credible Interval)].

Treatment	Placebo	ALN[10]	ETI	RIS	ZOL
Placebo	--	--	--	--	--
ALE[10]	0.52 (0.26, 1.01)	--	--	--	--
ETI	0.98 (0.15, 5.84)	1.90 (0.27, 12.77)	--	--	--
RIS	0.74 (0.51, 1.08)	1.42 (0.67, 3.06)	0.75 (0.12, 4.97)	--	--
ZOL	**0.58 (0.36, 0.94)**	1.12 (0.50, 2.56)	0.59 (0.093, 3.98)	0.79 (0.43, 1.45)	--

Note: ALE[10], alendronate 10 mg/day po (70 mg/week); ETI, 400 mg/month po; RIS, risedronate 150 mg/month po; ZOL, zoledronic acid 5 mg/year iv. Statistically significant results are in bold font.

Eleven studies[136,140,145,147,152,156,157,159,162-164] had hip fracture outcome data that could be assessed and were included in the analysis (total participants 13 674). All studies compared the various bisphosphonates to placebo, and there were no studies that compared bisphosphonates to each other. Figure 9c shows the network diagram for hip fractures.

The analysis showed that only zoledronic acid (OR 0.58; 95% CrI 0.36, 0.94) is effective at preventing hip fractures compared to placebo (Table 12c). Of note, the results for alendronate 10 mg/day po almost reached significance compared to placebo (OR 0.52; 95% CrI 0.26, 1.01), risedronate was the next most effective. The comparisons of each bisphosphonate to each other did not reveal that any bisphosphonate was more effective at preventing hip fractures.

Figure 9d. Network diagram for wrist fractures.

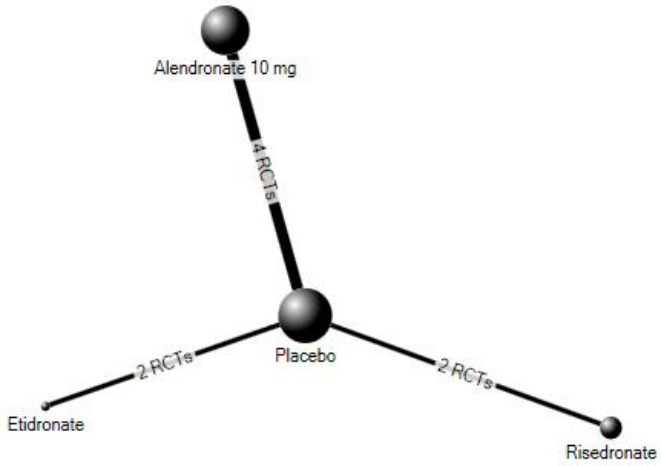


Table 12d. Bayesian MTC for bisphosphonates: Wrist fractures. [Odds Ratio (95% Credible Interval)].

Treatment	Placebo	ALN[10]	ETI	RIS
Placebo	--	--	--	--
ALE[10]	0.73 (0.39, 1.12)	--	--	--
ETI	2.29 (0.36, 19.9)	3.18 (0.47, 30.29)	--	--
RIS	0.61 (0.24, 1.49)	0.84 (0.31, 2.55)	0.27 (0.026, 2.05)	--

Note: ALE[10], alendronate 10 mg/day po (70 mg/week); ETI, 400 mg/month po; ZOL, zoledronic acid 5 mg/year iv.

Eight studies[140,142,145,147,152,157,160,161] reported wrist fracture outcome data that could be assessed and were included in the analysis (total participants 11 048). All studies compared the various bisphosphonates to placebo, and there were no studies that compared bisphosphonates to each other. Figure 9d shows the network diagram for wrist fractures.

The analysis showed that none of the bisphosphonates were effective at preventing wrist fractures compared with placebo or each other (Table 12d). However, only eight studies could be included in this analysis and this limits the conclusions that can be drawn.

Figure 9e. Network diagram for total withdrawals.

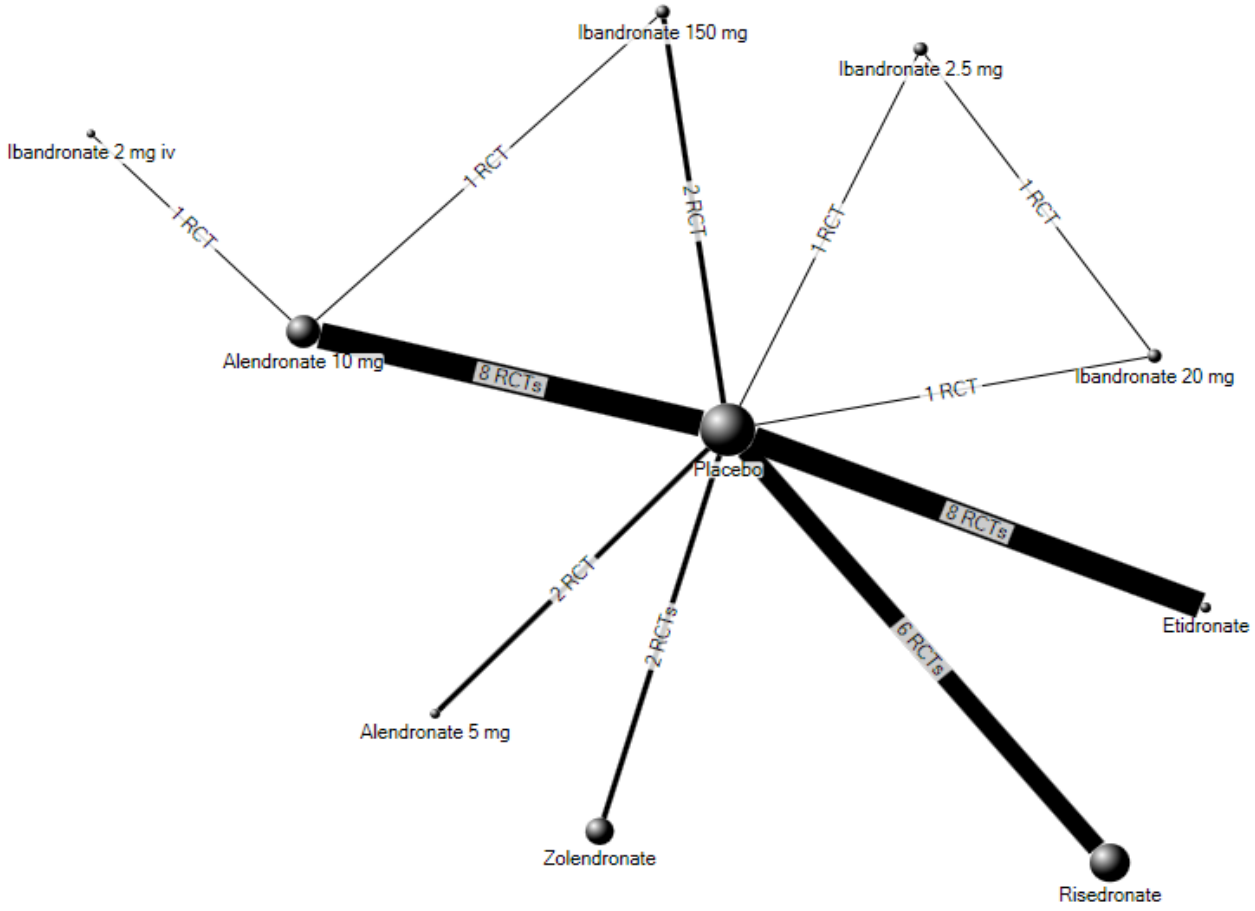


Table 12e. Bayesian MTC for bisphosphonates: Total withdrawals. [Odds Ratio (95% Credible Interval)].

Treatment	Placebo	ALN^{5}	ALN^{10}	ETI	IBA^{2}	IBA^{150}	IBA$^{2.5}$	IBA^{20}	RIS	ZOL
Placebo	--	--	--	--	--	--	--	--	--	--
ALE^{5}	1.13 (0.32, 4.06)	--	--	--	--	--	--	--	--	--
ALE^{10}	0.75 (0.46, 1.24)	0.66 (0.17, 2.59)	--	--	--	--	--	--	--	--
ETI	0.92 (0.50, 1.67)	0.81 (0.20, 3.28)	1.23 (0.56, 2.64)	--	--	--	--	--	--	--
IBA^{2}	1.05 (0.13, 9.09)	0.92 (0.082, 11.22)	1.40 (0.19, 11.42)	1.14 (0.13, 10.84)	--	--	--	--	--	--
IBA^{150}	1.18 (0.41, 3.67)	1.05 (0.20, 5.76)	1.58 (0.57, 4.64)	1.29 (0.39, 4.68)	1.14 (0.11, 11.23)	--	--	--	--	--
IBA$^{2.5}$	0.92 (0.27, 3.22)	0.81 (0.14, 4.87)	1.24 (0.32, 4.68)	1.01 (0.25, 4.05)	0.89 (0.074, 9.88)	0.78 (0.14, 3.96)	--	--	--	--
IBA^{20}	0.86 (0.25, 2.99)	0.76 (0.13, 4.53)	1.16 (0.30, 4.38)	0.94 (0.24, 3.77)	0.83 (0.068, 9.21)	0.73 (0.13, 3.70)	0.94 (0.27, 3.24)	--	--	--
RIS	0.82 (0.47, 1.42)	0.72 (0.18, 2.86)	1.10 (0.51, 2.27)	0.89 (0.39, 2.01)	0.78 (0.084, 6.68)	0.69 (0.19, 2.26)	0.89 (0.22, 3.45)	0.95 (0.24, 3.68)	--	--
ZOL	0.96 (0.31, 3.02)	1.29 (0.36, 4.45)	0.85 (0.15, 4.70)	1.05 (0.29, 3.83)	0.92 (0.081, 9.75)	0.81 (0.16, 3.83)	1.04 (0.19, 5.68)	1.11 (0.21, 6.04)	1.18 (0.33, 4.20)	--

Note: ALE^{5}, alendronate 5 mg/day po (35 mg/week); ALE^{10}, alendronate 10 mg/day po (70 mg/week) ; ETI, 400 mg/month po; IBA^{2}, ibandronate 2 mg/every 3 months iv; IBA^{150}, ibandronate 150 mg/month po; IBA$^{2.5}$, 2.5 mg/day po; IBA^{20}, 20 mg/day po intermittently; RIS, risedronate 150 mg/month po; ZOL, zoledronic acid 5 mg/year iv.

Twenty-nine studies[62,108,118,120,121,136,140-142,144-148,150-161] reported total withdrawal outcome data that could be assessed and were included in the analysis (total participants 35 644). There were three trials that included comparisons between bisphosphonates: the first trial compared alendronate 10 mg/day po to ibandronate 2 mg every 3 months iv[121], the second trial[62] compared alendronate 10 mg/day po to ibandronate 150 mg/month po and placebo, and the third trial compared ibandronate 2.5 mg/day po to ibandronate 20 mg intermittently po and placebo[118]. All other studies compared various bisphosphonates to placebo. Figure 9e shows the network diagram for total withdrawals.

Total withdrawals and adverse event withdrawals were assessed to provide a crude indicator of safety concerns. The analysis showed that none of the bisphosphonates appear to result in more withdrawals from treatment compared to placebo or each other (Table 12e). Odds ratios versus placebo were close to 1 and ranged from 0.75 to 1.18, but all credibility intervals crossed 1.

Figure 9f. Network diagram for adverse event withdrawals.

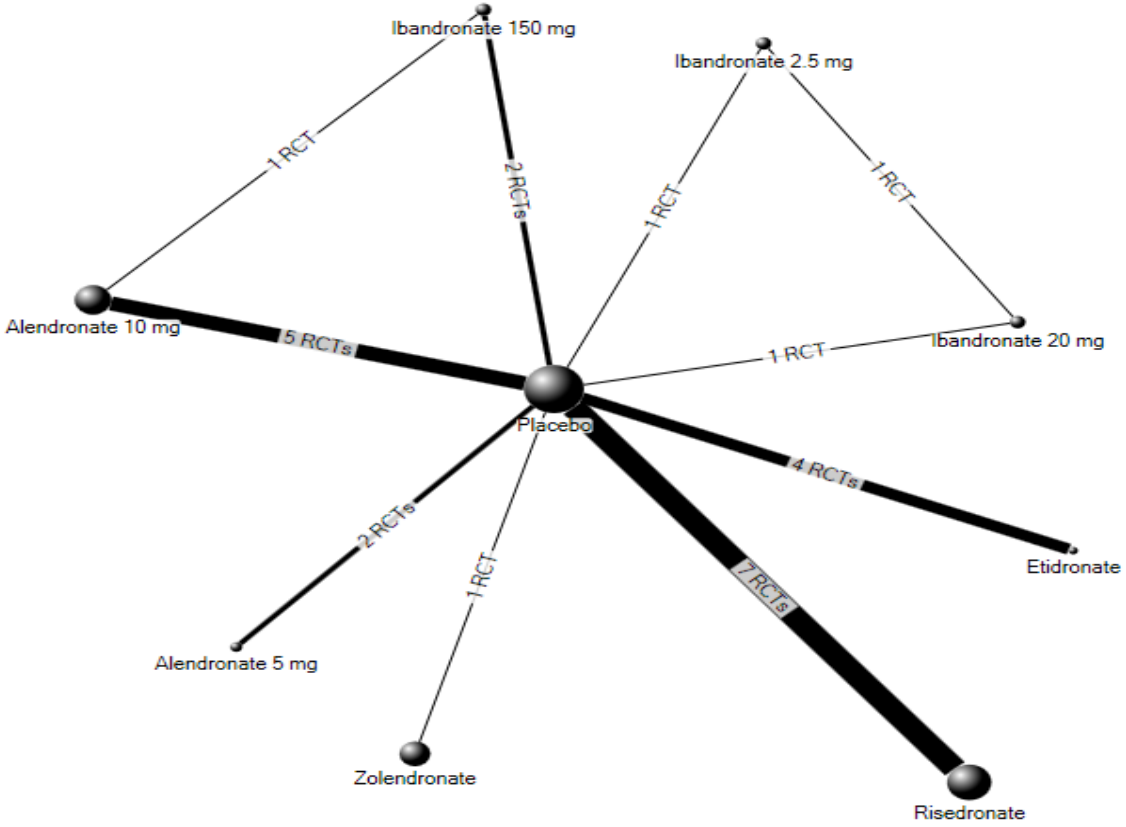


Table 12f. Bayesian MTC for bisphosphonates: Adverse event withdrawals. [Odds Ratio (95% Credible Interval)].

Treatment	Placebo	ALN^{5}	ALN^{10}	ETI	IBA^{150}	IBA$^{2.5}$	IBA^{20}	RIS	ZOL
Placebo	--	--	--	--	--	--	--	--	--
ALE^{5}	1.02 (0.34, 3.03)	--	--	--	--	--	--	--	--
ALE^{10}	0.97 (0.48, 1.96)	0.95 (0.26, 3.51)	--	--	--	--	--	--	--
ETI	1.02 (0.40, 2.63)	1.00 (0.24, 4.28)	1.06 (0.33, 3.43)	--	--	--	--	--	--
IBA^{150}	1.41 (0.42, 5.07)	1.38 (0.28, 7.520	1.46 (0.46, 4.88)	1.37 (0.30, 6.70)	--	--	--	--	--
IBA$^{2.5}$	0.92 (0.23, 3.60)	0.90 (0.16, 5.21)	0.95 (0.20, 4.39)	0.90 (o.17, 4.77)	0.66 (0.098, 3.98)	--	--	--	--
IBA^{20}	0.86 (0.22, 3.42)	0.84 (0.14, 4.94)	0.89 (0.19, 4.16)	0.84 (0.16, 4.53)	0.61 (0.092, 3.77)	0.93 (0.24, 3.70)	--	--	--
RIS	0.93 (0.51, 1.70)	0.91 (0.27, 3.22)	0.96 (0.38, 2.43)	0.91 (0.30, 2.81)	0.66 (0.16, 2.52)	1.01 (0.23, 4.59)	1.08 (0.24, 4.91)	--	--
ZOL	1.16 (0.29, 4.62)	1.13 (0.20, 6.79)	1.20 (0.25, 5.67)	1.13 (0.21, 6.03)	0.82 (0.12, 5.11)	1.26 (0.18, 9.06)	1.35 (0.19, 9.62)	1.25 (0.28, 5.60)	--

Note: ALE^{5}, alendronate 5 mg/day po (35 mg/week); ALE^{10}, alendronate 10 mg/day po (70 mg/week); ETI, 400 mg/month po; IBA^{150}, ibandronate 150 mg/month po; IBA$^{2.5}$, 2.5 mg/day po; IBA^{20}, 20 mg/day po intermittently; RIS, risedronate 150 mg/month po; ZOL, zoledronic acid 5 mg/year iv.

Twenty-five studies[62,118,120,121,136,140,142,144-154, 156-161] reported adverse event withdrawal outcome data that could be assessed and were included in the analysis (total participants 35 416). There were two trials that included comparisons between bisphosphonates: one trial[62] compared alendronate 10 mg/day po to ibandronate 150 mg/month po and placebo, and the other trial compared ibandronate 2.5 mg/day po to ibandronate 20 mg intermittently po and placebo[118]. All other studies compared various bisphosphonates to placebo. Figure 9f shows the network diagram for adverse event withdrawals.

The analysis showed that none of the bisphosphonates appear to result in more withdrawals from treatment due to adverse events compared to placebo or each other (Table 12f). Odds ratios versus placebo ranged from 0.86 to 1.41, but all credibility intervals crossed 1.

Table 13. Number needed to treat for benefit (B) or harm (H) for bisphosphonates versus placebo for various outcomes (values generated from statistically significant results are bolded).

Treatment	Vertebral Fractures	Non-vertebral Fractures	Hip Fractures	Wrist Fractures	Total Withdrawals	Adverse Event Withdrawals
Alendronate 5 mg/day po	33 (B)	561 (H)	N/A	N/A	40 (H)	486 (H)
Alendronate 10 mg/day po	**27 (B)**	**50 (B)**	949 (B)	136 (B)	19 (B)	322 (B)
Etidronate 400 mg/month po	**23 (B)**	33 (B)	22777 (B)	30 (H)	60 (B)	486 (H)
Ibandronate 2 mg/every 3 months iv	N/A	62 (B)	N/A	N/A	N/A	N/A
Ibandronate 150 mg/month po	**25 (B)**	124 (B)	N/A	N/A	100 (H)	25 (H)
Ibandronate 2.5 mg/day po	**24 (B)**	101(B)	N/A	N/A	29 (H)	120 (B)
Ibandronate 20 mg intermittently po	**25 (B)**	141 (H)	N/A	N/A	60 (B)	69 (B)
Risedronate 150 mg/month	**31 (B)**	**44 (B)**	1752 (B)	94 (B)	26 (B)	138 (B)
Zoledronic acid 5 mg/year iv	**17 (B)**	41 (B)	**1084 (B)**	N/A	122 (H)	62 (H)

Odds ratios and the placebo group event rates were used to calculate the number needed to benefit (NNB) or harm (NNH) (Table 13). Caution should be exercised when interpreting these values as not all the odds ratio results were significant and therefore results could range from a NNB to a NNH.

For vertebral fractures, results obtained for all the bisphosphonates generated a NNB that ranged from 17 to 33, with zoledronic acid having the lowest value. Non-vertebral fracture results generated NNB for all but two therapies, alendronate 5 mg/day po and ibandronate 20 mg intermittently po, which generated high NNH values.

The lowest NNB for hip fracture results was for alendronate 10 mg/day po (949), but this value was still quite high at and was not from a statistically significant odds ratio. The NNB for zoledronic acid was 1084 and was derived from a statistically significant odds ratio. The higher values seen for hip fractures compared to vertebral or non-vertebral fractures is likely due to their rarer occurrence, and studies were not designed or powered with hip fractures as main outcomes.

Only three products had data for wrist fractures and the results generated both NNB (alendronate 10 mg/day po and etidronate 400 mg/month po) and NNH (risedronate 150 mg/month po) values. Again, there were fewer studies in the wrist fracture analysis results were not statistically significant, and studies were not designed with these as main outcomes.

For both total and adverse event withdrawals, NNB and NNH values were generated. Alendronate 10 mg/day po appears to be the most beneficial product for both of these outcomes with an NNB of 19 for total withdrawals and 322 for adverse event withdrawals, however the odds ratios were not statistically significant.

5.3.3 Mixed treatment comparisons – frequentist analysis

The following tables show the results for the frequentist analytical approach generated using SAS (random effects model) for each treatment compared with placebo for vertebral and non-vertebral fractures as well as total and adverse event withdrawals (all treatment comparisons are not shown for space considerations). For comparison, the results of the Bayesian MTC analyses are shown.

Table 14a. Frequentist and Bayesian MTCs for bisphosphonates versus placebo: Vertebral fractures.

Treatment	Frequentist analysis OR (95% CI)[a]	Bayesian analysis OR (95% CrI)[b]
Alendronate 5 mg/day po	0.61 (0.16, 2.26)	0.62 (0.15, 2.37)
Alendronate 10 mg/day po	**0.51 (0.41, 0.65)**	**0.53 (0.40, 0.71)**
Etidronate 400 mg/month po	**0.44 (0.22, 0.89)**	**0.47 (0.23, 0.94)**
Ibandronate 150 mg/month po	0.36 (0.11, 1.18)	0.51 (0.13, 1.96)
Ibandronate 2.5 mg/day po	**0.49 (0.32, 0.74)**	**0.49 (0.30, 0.79)**
Ibandronate 20 mg intermittently po	**0.51 (0.34, 0.78)**	**0.51 (0.32, 0.83)**
Risedronate 150 mg/month po	**0.60 (0.47, 0.76)**	**0.59 (0.48, 0.78)**
Zoledronic acid 5 mg/year iv	**0.28 (0.18, 0.36)**	**0.28 (0.20, 0.40)**

[a]OR (95% CI), Odds Ratio (95% Confidence Interval); [b]OR (95% CrI), Odds Ratio (95% Credible Interval). Significant results are in bold font.

Table 14b. Frequentist and Bayesian MTCs for bisphosphonates versus placebo : Non-vertebral fractures.

Treatment	Frequentist analysis OR (95% CI)[a]	Bayesian analysis OR (95% CrI)[b]
Alendronate 5 mg/day po	1.04 (0.62, 1.76)	1.02 (0.58, 1.78)
Alendronate 10 mg/day po	**0.79 (0.69, 0.91)**	**0.78 (0.59, 0.95)**
Etidronate 400 mg/month po	0.77 (0.47, 1.27)	0.67 (0.40, 1.10)
Ibandronate 2 mg/every 3 months iv	0.36 (0.037, 3.53)	0.82 (0.013, 46.85)
Ibandronate 150 mg/month po	0.75 (0.38, 1.50)	0.91 (0.41, 2.08)
Ibandronate 2.5 mg/day po	1.12 (0.81, 1.54)	1.11 (0.72, 1.69)
Ibandronate 20 mg intermittently po	1.09 (0.79, 1.50)	1.08 (0.70, 1.65)
Risedronate 150 mg/month po	**0.78 (0.69, 0.89)**	**0.75 (0.57, 0.91)**
Zoledronic acid 5 mg/year iv	**0.73 (0.62, 0.86)**	0.78 (0.53, 1.02)

[a]OR (95% CI), Odds Ratio (95% Confidence Interval); [b]OR (95% CrI), Odds Ratio (95% Credible Interval). Significant results are in bold font.

Table 14c. Frequentist and Bayesian MTCs for bisphosphonates versus placebo: Hip fractures.

Treatment	Frequentist analysis OR (95% CI)[a]	Bayesian analysis OR (95% CrI)[b]
Alendronate 10 mg/day po	**0.48 (0.25, 0.90)**	0.52 (0.26, 1.01)
Etidronate 400 mg/month po	1.02 (0.24, 4.28)	0.98 (0.15, 1.08)
Risedronate 150 mg/month po	**0.74 (0.57, 0.97)**	0.74 (0.51, 1.08)
Zoledronic acid 5 mg/year iv	**0.59 (0.41, 0.85)**	**0.58 (0.36, 0.94)**

[a]OR (95% CI), Odds Ratio (95% Confidence Interval); [b]OR (95% CrI), Odds Ratio (95% Credible Interval). Significant results are in bold font.

Table 14d. Frequentist and Bayesian MTCs for bisphosphonates versus placebo: Wrist factures.

Treatment	Frequentist analysis OR (95% CI)[a]	Bayesian analysis OR (95% CrI)[b]
Alendronate 10 mg/day po	0.86 (0.65, 1.14)	0.73 (0.39, 1.12)
Etidronate 400 mg/month po	1.65 (0.39, 7.01)	2.29 (0.36, 19.9)
Risedronate 150 mg/month po	0.63 (0.31, 1.30)	0.61 (0.24, 1.49)

[a]OR (95% CI), Odds Ratio (95% Confidence Interval); [b]OR (95% CrI), Odds Ratio (95% Credible Interval)

Table 14e. Frequentist and Bayesian MTCs for bisphosphonates versus placebo: Total withdrawals.

Treatment	Frequentist analysis OR (95% CI)[a]	Bayesian analysis OR (95% CrI)[b]
Alendronate 5 mg/day po	1.13 (0.82, 1.56)	1.13 (0.32, 4.06)
Alendronate 10 mg/day po	1.03 (0.91, 1.16)	0.75 (0.46, 1.24)
Etidronate 400 mg/month po	0.95 (0.66, 1.36)	0.92 (0.50, 1.67)
Ibandronate 2 mg/every 3 months iv	0.76 (0.21, 2.75)	1.05 (0.13, 9.09)
Ibandronate 150 mg/month po	1.11 (0.82, 1.50)	1.18 (0.41, 3.67)
Ibandronate 2.5 mg/day po	0.93 (0.77, 1.12)	0.92 (0.27, 3.22)
Ibandronate 20 mg intermittently po	0.87 (0.72, 1.06)	0.86 (0.25, 2.99)
Risedronate 150 mg/month po	0.93 (0.86, 1.01)	0.82 (0.47, 1.42)
Zoledronic acid 5 mg/year iv	0.96 (0.87, 1.06)	0.96 (0.31, 3.02)

[a]OR (95% CI), Odds Ratio (95% Confidence Interval); [b]OR (95% CrI), Odds Ratio (95% Credible Interval)

Table 14f. Frequentist and Bayesian MTCs for bisphosphonates versus placebo: Adverse event withdrawals.

Treatment	Frequentist analysis OR (95% CI)[a]	Bayesian analysis OR (95% CrI)[b]
Alendronate 5 mg/day po	1.24 (0.81, 1.90)	1.02 (0.34, 3.03)
Alendronate 10 mg/day po	0.96 (0.84, 1.11)	0.97 (0.48, 1.96)
Etidronate 400 mg/month po	0.81 (0.44, 1.50)	1.02 (0.40, 2.63)
Ibandronate 150 mg/month po	1.00 (0.66, 1.54)	1.41 (0.42, 5.07)
Ibandronate 2.5 mg/day po	0.98 (0.77, 1.24)	0.92 (0.23, 3.60)
Ibandronate 20 mg intermittently po	1.00 (0.79, 1.27)	0.86 (0.22, 3.42)
Risedronate 150 mg/month po	0.97 (0.88, 1.08)	0.93 (0.51, 1.70)
Zoledronic acid 5 mg/year iv	1.15 (0.93, 1.41)	1.16 (0.29, 4.62)

[a]OR (95% CI), Odds Ratio (95% Confidence Interval); [b]OR (95% CrI), Odds Ratio (95% Credible Interval)

The results for the frequentist analyses using SAS (random effects model) for all the outcomes are presented in Tables 14a-f. Odds ratios and CIs were very similar to ORs and CrIs obtained through the Bayesian analyses using WinBUGS. Confidence intervals were consistently narrower than CrIs, and in some cases resulted in results becoming statistically significant: for non-vertebral fractures zoledronic acid 5 mg/year iv the results was significant (OR 0.73, 95% CrI 0.62, 0.86), and for the prevention of hip fractures the results for alendronate 10 mg/day po (OR 0.48, 95% CrI 0.25, 0.90), risedronate 150 mg/month po (OR 0.74, 95% CrI 0.57, 0.97), and zoledronic acid 5 mg/year iv (OR 0.59, 95% CrI 0.41, 0.85) were significant. Frequentist analyses were also conducted using fixed effects models for all outcomes and subgroups and results were again consistent with those derived from the Bayesian analyses fixed effects models.

5.3.4 Subgroup Analyses

Subgroup analyses were performed to examine the following: outcomes in trials greater than or equal to 3 years or less than 3 years in duration, and outcomes in primary and secondary prevention trials.

5.3.4.1 Outcomes by trial duration

Table 15a. Bisphosphonates versus placebo, ≥ 3 years and < 3 years: Vertebral fractures.

Treatment	≥ 3 years		< 3 years	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	N/A	N/A	0.62 (0.14, 2.42)	1
Alendronate 10 mg/day po	**0.51 (0.38, 0.69)**	2	0.79 (0.29, 2.11)	2
Etidronate 400 mg/month po	**0.35 (0.12, 0.86)**	3	0.69 (0.23, 2.05)	3
Ibandronate 150 mg/month po	N/A	N/A	0.75 (0.14, 4.06)	1
Ibandronate 2.5 mg/day	**0.49 (0.29, 0.79)**	1	N/A	N/A
Ibandronate 20 mg intermittently po	**0.51 (0.31, 0.84)**	1	N/A	N/A
Risedronate 150 mg/month po	**0.58 (0.42, 0.80)**	2	0.64 (0.32, 1.28)	2
Zoledronic acid 5 mg/year iv	**0.28 (0.19, 0.40)**	1	N/A	N/A

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 15b. Bisphosphonates versus placebo, ≥ 3 years and < 3 years: Non-vertebral fractures.

Treatment	≥ 3 years		< 3 years	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	N/A	N/A	1.01 (0.55, 1.82)	2
Alendronate 10 mg/day po	0.84 (0.65, 1.07)	2	**0.48 (0.26, 0.86)**	6
Etidronate 400 mg/month po	0.72 (0.27, 1.85)	3	0.64 (0.33, 1.20)	4
Ibandronate 2 mg/every 3 months iv	N/A	N/A	0.49 (0.01, 24.68)	1
Ibandronate 150 mg/ month po	N/A	N/A	0.61 (0.24, 1.60)	2
Ibandronate 2.5 mg/day po	1.11 (0.74, 1.67)	1	N/A	N/A
Ibandronate 20 mg intermittently po	1.08 (0.72, 1.64)	1	N/A	N/A
Risedronate 150 mg/month po	**0.76 (0.50, 0.94)**	3	0.59 (0.28, 1.22)	3
Zoledronic acid 5 mg/year iv	0.73 (0.53, 1.00)	1	1.02 (0.03, 45.36)	1

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 15c. Bisphosphonates versus placebo, ≥ 3 years and < 3 years: Hip fractures.

Treatment	≥ 3 years		< 3 years	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 10 mg/day po	0.47 (0.20, 1.07)	1	0.58 (0.18, 1.90)	4
Etidronate 400 mg/month po	0.64 (0.07, 4.60)	2	Data not usable	1
Risedronate 150 mg/month po	0.74 (0.50, 1.09)	2	N/A	N/A
Zoledronic acid 5 mg/year iv	**0.58 (0.35, 0.95)**	1	N/A	N/A

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 15d. Bisphosphonates versus placebo, ≥ 3 years and < 3 years: Wrist fractures.

Treatment	≥ 3 years		< 3 years	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 10 mg/day po	0.87 (0.49, 1.41)	2	**0.33 (0.11, 0.86)**	2
Etidronate 400 mg/month po	1.03 (0.10, 10.49)	1	Data not useable	1
Risedronate 150 mg/month po	0.62 (0.24, 1.54)	1	0.52 (0.01, 18.82)	1

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 15e. Bisphosphonates versus placebo, ≥ 3 years and < 3 years: Total withdrawals.

Treatment	≥ 3 years		< 3 years	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	N/A	N/A	1.14 (0.25, 5.24)	1
Alendronate 10 mg/day po	1.13 (0.89, 1.44)	2	0.63 (0.32, 1.31)	8
Etidronate 400 mg/month po	0.68 (0.38, 1.22)	4	1.20 (0.46, 3.08)	4
Ibandronate 2 mg iv every 3 months	N/A	N/A	0.89 (0.09, 9.78)	1
Ibandronate 150 mg/month po	N/A	N/A	1.11 (0.32, 4.33)	1
Ibandronate 2.5 mg/day po	0.92 (0.66, 1.29)	1	N/A	N/A
Ibandronate 20 mg intermittently po	0.86 (0.62, 1.21)	1	N/A	N/A
Risedronate 150 mg/month po	0.88 (0.71, 1.05)	3	0.77 (0.27, 2.07)	3
Zoledronic acid 5 mg/year iv	0.96 (0.71, 1.29)	1	0.98 (0.02, 51.1)	1

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval).

Table 15f. Bisphosphonates versus placebo, ≥ 3 years and < 3 years: Adverse event withdrawals.

Treatment	≥ 3 years		< 3 years	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	N/A	N/A	1.01 (0.27, 3.56)	2
Alendronate 10 mg/day po	0.90 (0.69, 1.15)	2	0.52 (0.20, 1.42)	4
Etidronate 400 mg/month po	0.77 (0.29, 2.04)	3	1.67 (0.37, 8.35)	4
Ibandronate 150 mg/month po	N/A	N/A	0.97 (0.24, 4.63)	1
Ibandronate 2.5 mg/day po	0.96 (0.68, 1.38)	1	N/A	N/A
Ibandronate 20 mg intermittently po	0.98 (0.69, 1.40)	1	N/A	N/A
Risedronate 150 mg/month po	0.95 (0.76, 1.14)	3	0.97 (0.35, 2.74)	4
Zoledronic acid 5 mg/year iv	1.16 (0.83, 1.63)	1	N/A	N/A

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

All outcomes were assessed by treatment duration (Tables 15a-f). The efficacy of bisphosphonate treatment for fracture prevention in some cases was enhanced by longer treatment duration, however this was not the case for every fracture outcome.

For vertebral fractures efficacy improved for all therapies with longer duration (Table 15a). No therapy was significantly effective in trials that had a duration of less than 3 years.

Increasing trial length improved the efficacy of prevention of non-vertebral fractures (Table 15b) for risedronate 150 mg/month po only (OR 0.76, 95% CrI 0.50, 0.94), whereas alendronate 10 mg/day po was effective in trials with a duration less than 3 years (OR 0.48, 95% CrI 0.68, 0.86).

Only zoledronic acid was effective at 3 years or longer at preventing hip fracture (Table 15c), but this is driven by the one large study involving this therapy (Black 2007).

Not all therapies had both categories of duration of studies, for example there was only 1 trial that used ibandronate 2 mg every 3 months iv (< 3 years), so not all comparisons were possible. The overall small number of trials that had hip and wrist fracture outcomes

frequently resulted in only 1 trial or 0 trials in each category, limiting the comparison of trial duration (Tables 15c and d).

Total and adverse withdrawal outcomes (Tables 15 e and f) did not show a general trend regarding duration of treatment with bisphosphonates; for some therapies longer duration increased the odds of treatment withdrawal while this was the opposite for other therapies. This is possibly due to the small number of studies in each category for most therapies, as the maximum number of studies in each category was 4 with the exception of studies less than 3 years using alendronate 10 mg/day po, which had 8 studies.

5.3.4.2 Outcomes by secondary and primary prevention trials

All outcomes were assessed for secondary and primary prevention trials, except for hip fracture as all the included trials with that outcome were secondary prevention trials.

Table 16a. Bisphosphonates versus placebo, secondary and primary prevention studies: Vertebral fractures.

Treatment	Secondary prevention		Primary prevention	
	OR (95% CrI)[a]	Number of studies	OR (95% CrI)	Number of studies
Alendronate 5 mg/day po	0.64 (0.14, 2.55)	1	N/A	N/A
Alendronate 10 mg/day po	**0.52 (0.36, 0.78)**	3	**0.54 (0.31, 0.95)**	1
Etidronate 400 mg/month po	**0.38 (0.17, 0.79)**	4	N/A[b]	2
Ibandronate 150 mg/month po	0.50 (0.12, 2.09)	1	N/A	N/A
Ibandronate 2.5 mg/ day po	**0.49 (0.29, 0.80)**	1	N/A	N/A
Ibandronate 20 mg intermittently po	**0.51 (0.31, 0.82)**	1	N/A	N/A
Risedronate 150 mg/month po	**0.57 (0.41, 0.76)**	3	0.97 (0.35, 2.75)	1
Zoledronic acid 5 mg/year iv	**0.28 (0.19, 0.40)**	1	N/A	N/A

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval); [b]Zero events resulted in uninterpretable results. Significant results are in bold font.

Table 16b. Bisphosphonates versus placebo, secondary and primary prevention studies: Non-vertebral fractures.

Treatment	Secondary prevention		Primary prevention	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	1.03 (0.61, 1.75)	2	N/A	N/A
Alendronate 10 mg/day po	**0.71 (0.56, 0.89)**	7	0.56 (0.87, 1.36)	1
Etidronate 400 mg/month po	0.71 (0.40, 1.22)	5	0.51 (0.14, 1.65)	2
Ibandronate 2 mg/every 3 months iv	0.70 (0.017, 28.87)	1	N/A	N/A
Ibandronate 150 mg/month po	0.82 (0.36, 1.88)	1	1.11(0.11, 11.52)	1
Ibandronate 2.5 mg daily po	1.11 (0.81, 1.52)	1	N/A	N/A
Ibandronate 20 mg intermittently po	1.08 (0.79, 1.49)	1	N/A	N/A
Risedronate 150 mg/month po	**0.79 (0.69, 0.89)**	4	0.69 (0.21, 2.15)	2
Zoledronic acid 5 mg/year iv	**0.73 (0.62, 0.85)**	1	0.94 (0.014, 43.74)	1

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 16c. Bisphosphonates versus placebo, secondary and primary prevention studies: Wrist fractures.

Treatment	Secondary prevention		Primary prevention	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 10 mg/day po	**0.46 (0.26, 0.76)**	3	1.20 (0.70, 2.05)	1
Etidronate 400 mg/month po	2.20 (0.40, 17.03)	2	N/A	N/A
Risedronate 150 mg/month po	0.62 (0.27, 1.35)	1	0.46 (0.010, 17.88)	1

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 16d. Bisphosphonates versus placebo, secondary and primary prevention studies: Total withdrawals.

Treatment	Secondary prevention		Primary prevention	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	1.13 (0.28, 4.69)	1	N/A	N/A
Alendronate 10 mg/day po	**0.69 (0.36, 0.76)**	8	1.08 (0.75, 1.52)	2
Etidronate 400 mg/month po	0.83 (0.52, 1.37)	5	1.27 (0.63, 2.62)	3
Ibandronate 2 mg/every 3 months iv	0.96 (0.11, 9.81)	1	N/A	N/A
Ibandronate 150 mg/month po	0.75 (0.16, 3.68)	1	2.86 (0.73, 14.94)	1
Ibandronate 2.5 mg/day po	0.92 (0.23, 3.74)	1	N/A	N/A
Ibandronate 20 mg intermittently po	0.86 (0.21, 3.47)	1	N/A	N/A
Risedronate 150 mg/month po	0.84 (0.42, 1.63)	5	0.71 (0.35, 1.39)	1
Zoledronic acid 5 mg/year iv	0.96 (0.24, 3.82)	1	1.00 (0.020, 42.57)	1

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval). Significant results are in bold font.

Table 16e. Bisphosphonates versus placebo, secondary and primary prevention studies: Adverse event withdrawals.

Treatment	Secondary prevention		Primary prevention	
	OR (95% CrI)[a]	**Number of studies**	**OR (95% CrI)**	**Number of studies**
Alendronate 5 mg/day po	1.25 (0.81, 1.94)	1	N/A	N/A
Alendronate 10 mg/day po	0.90 (0.68, 1.19)	8	0.89 (0.51, 1.28)	2
Etidronate 400 mg/month po	0.67 (0.20, 2.15)	3	3.81 (0.72, 35.53)	3
Ibandronate 150 mg/month po	0.93 (0.56, 1.56)	1	2.93 (0.69, 16.02)	1
Ibandronate 2.5 mg/day po	0.92 (0.77, 1.11)	1	N/A	N/A
Ibandronate 20 mg intermittently po	0.86 (0.72, 1.04)	1	N/A	N/A
Risedronate 150 mg/month po	0.97 (0.88, 1.07)	5	0.66 (0.29, 1.44)	2
Zoledronic acid 5 mg/year iv	1.16 (0.94, 1.42)	1	N/A	N/A

[a]OR (95% CrI), Odds Ratio (95% Credibility Interval)

For all outcomes and therapies the majority of trials were secondary prevention studies; often there were only 1 or 0 primary prevention trials for each therapy. The exceptions was alendronate 10 mg/day po, etidronate 400 mg/month po, and risedronate 150

mg/month po, for which there were at least 2 trials in each prevention category for some outcomes (Tables 16a-f).

Most trials with vertebral fractures as an outcome were secondary prevention trials (13 out of 17 trials). Alendronate 10 mg/day po was the only therapy that appears efficacious for primary prevention as well as secondary prevention for vertebral fractures and the OR was similar in both types of trials (Table 16a; OR 0.52, 95% CrI 0.36, 0.78 for the secondary prevention trials and OR 0.54, 95% CrI 0.31,0.85 for the primary prevention trial).

For non-vertebral fracture prevention, alendronate 10 mg/day po, risedronate 150 mg/month po, and zoledronic acid 5 mg/year iv were efficacious at preventing these fractures when used for secondary prevention but not for primary prevention (Table 16b). All the studies that examined hip fractures as an outcome were secondary prevention studies so no data was available to examine primary prevention for this outcome.
For wrist fractures, alendronate 10 mg/day po was efficacious in the secondary prevention (Table 16c; OR 0.46, 95% CrI 0.26, 0.76) setting but not for primary prevention (OR 1.20, 95% CrI 0.70, 2.05).

Compared with placebo, alendronate 10 mg/day po had an OR of 0.69 (95% CrI 0.36, 0.76) for total withdrawals in secondary prevention trials, and had the only significant result for this outcome (Table 16e). This was not seen in the original analysis for total withdrawals where the OR was 0.75 (95% CrI 0.46, 1.24). No significant results were seen in either type of prevention trial for adverse event withdrawals (Table 16f).

5.3.5 Sensitivity analyses

Sensitivity analyses were conducted that examined the differences in results between: 1) baseline denominators at study enrollment and follow-up denominators, and 2) random and fixed effects models.

The results from the analyses of baseline and follow-up denominators are presented in Appendix 12. The results were consistent and indicate that the drop-outs from the trials were similar across treatments and are an unlikely source of bias.

Random and fixed effects model analyses are presented in Appendix 12. Again, results were consistent, although the credibility intervals were, as expected, narrower for the fixed effect model results given that this model assumes a true fixed effect that is common to all the studies. The choice of model did not change whether a result was statistically significant or not.

5.4 Discussion

5.4.1 Summary of Results

All the treatments assessed (with the exception of alendronate 5 mg/day po and ibandronate 150 mg/month po), were effective at preventing vertebral fractures . Zoledronic acid 5 mg/year iv was found to be the most effective regarding vertebral fracture prevention. Zoledronic acid was significantly better at preventing vertebral fractures than alendronate 10 mg/day po, ibandronate 20 mg intermittently po, and risedronate 150 mg/month po.

Only alendronate 10 mg/day po and risedronate 150 mg/month po were found to be effective at preventing non-vertebral fractures compared to placebo. The results for zoledronic acid for non-vertebral fractures almost reached significance compared to placebo .The comparisons of each bisphosphonate to each other did not reveal that any bisphosphonate was more effective at preventing non-vertebral fractures.

Only zoledronic acid was found to be effective at preventing hip fractures compared to placebo. The results for alendronate 10 mg/day po for hip fracture prevention almost reached significance compared to placebo . The comparisons of each bisphosphonate to

each other did not reveal that any bisphosphonate was more effective at preventing hip fractures.

No bisphosphonate was found to be effective at preventing wrist fractures compared with placebo or each other, but only 8 studies were available to be included in this analysis.

None of the bisphosphonates resulted in more total withdrawals from treatment or adverse event withdrawals from clinical trials compared to placebo or each other.

5.4.2 Comparison to the literature

There have been three previously published studies that have compared the efficacy of bisphosphonates in fracture prevention using network meta-analysis methodologies[69-71].

The first of these studies[69] examined alendronate, ibandronate, risedronate, etidronate, and zoledronic acid and included only 8 studies (only studies with fracture endpoints were included). The outcomes examined were vertebral, non-vertebral and hip fractures. No safety outcomes were examined. The authors performed a Bayesian analysis and the outcome measure was relative risk. They concluded that zoledronic acid was the most effective therapy for fracture prevention versus placebo and the other therapies in the study, however they only presented the results of a fixed effect model, which would normally have narrower CrI and may have affected the results of some of the treatment comparisons. All of the treatments were effective for the prevention of vertebral fractures versus placebo with zoledronic acid being the most effective, risedronate was the most effective for preventing non-vertebral fractures and zoledronic acid was the best therapy for preventing hip fractures. The results were similar to those obtained from the current study, with the exception of alendronate at 10 mg/day po which was found to be effective for non-vertebral fracture prevention in the current study.

The study performed by Hopkins et al[70] included 30 studies and 9 drugs; denosumab, strontium, and teriparatide were also included and the outcomes examined were vertebral, non-vertebral, hip and wrist fractures. Studies were included if they included fractures as either primary or secondary outcomes. Both Bayesian and classical analyses were conducted using random effects models. For the bisphosphonates the authors concluded that all the drugs were effective at preventing vertebral fractures except etidronate, and that zoledronic acid was the most efficacious for this outcome. For non-vertebral fractures alendronate and risedronate were the only effective therapies and this is consistent with the results of the current study. Zoledronic acid was not found to be effective at preventing hip fractures in this study, which differs from the results of the first NMA[69] and the current study.

The final NMA study available for comparison[71] included 34 studies in total with the following treatments: alendronate, etidronate, ibandronate, risedronate, zoledronic acid, strontium, teriparatide, denusomab, and raloxifene. This study conducted a primary analysis with only studies that had fracture outcomes as endpoints, however the authors conducted a sensitivity analysis with studies that had fractures as adverse event outcomes. This study also used classical and Bayesian analytic techniques to conduct random effect analyses. The authors found that all the bisphosphonates with the exception of etidronate were effective at preventing vertebral fractures, that risedronate and zoledronic acid were the most effective for reducing non-vertebral and hip fractures, and that alendronate was effective at reducing non-vertebral fractures.

Generally the findings of the current study are consistent with previously published NMAs with respect to fracture prevention, with the exception of etidronate compared with placebo, as the current study found that etidronate was effective for preventing vertebral fractures. Tow of the previously published NMAs [70,71] did not find etidronate effective, likely because they included other studies that the current study did not and they also used vague rather than informative priors for the Bayesian analyses. Small differences in credibility intervals that change whether a result is significant or not may be the result of slightly different inclusion criteria (not all the previous studies included

RCTs with fracture as a secondary outcome), or the selection of the informative priors used in the construction of the models used in the Bayesian analysis.

5.4.2 Study limitations

The results of this network meta-analysis are believed to be robust as the review was performed according to the accepted methodology for systematic reviews and recommendations for the conduct of network meta-analysis. The literature search was comprehensive and included multiple databases and also searched reference lists to locate additional publications. In addition, inclusion and exclusion criteria were explicitly specified, a conservative data analysis using a random effects model was performed, and the results of the sensitivity analyses were consistent with the primary analyses. The initial search was updated to determine if newer publications were available, however none were identified that met the inclusion criteria.

However, there are several limitations to this type of study that must be considered when interpreting the results. These involve the different doses and routes of administration of the various bisphosphonates, the quality of fracture assessment and classification, the assessment of withdrawals and adverse events, and the large numbers of withdrawals in the larger and longer-term studies.

Bisphosphonates used for fracture prevention in osteoporosis therapies differ in terms of their dosage, dosing frequency, efficacy across fracture locations and route of administration. As discussed in Chapter 3, ibandronate was not used in the same doses and route of administration in all the studies that included it as an active comparator. In the RCTs included in this NMA, alendronate was used in two different oral doses, and zoledronic acid was administered intravenously. For ibandronate there was often only one trial per dose and they were small trials. Although there is a substantial population regarding zoledronic acid, the vast majority of that population is from a single study. Although the inclusion criteria stipulated that trials had to be conducted in women with

postmenopausal osteoporosis, there was a range of ages of study participants and those in primary prevention studies tended to be younger than those in the secondary prevention studies. These differences in the products and populations could have introduced some heterogeneity.

The unit of analysis for fracture outcomes was number of fractures over the study period, as opposed to the number of patients with a fracture. As a result there may have been a subset of patients more susceptible to fractures that may have affected the overall results, but this would not have been detected in this analysis.

The quality of fracture assessment and classification is another potential source of heterogeneity, particularly in studies where the primary endpoint was not fracture, but BMD or another endpoint. In particular, vertebral fractures may be unsymptomatic and be undetected unless they are being actively assessed using radiographs at different intervals. Non-vertebral fractures may or may not include hip fractures and not all trials classified non-vertebral fractures in the same way. There were a smaller number of trials that reported hip or wrist fractures, limiting the amount of data available for analyses of these outcomes and the results of the hip fracture analysis are dominated by one large study.

The subgroup analyses that examined the differences in outcomes depending on trial duration was limited by the number of studies for each therapy in each category (greater than or equal to 3 years or less than 3 years). However, for vertebral fracture prevention it does appear that treatment longer than 3 years with alendronate, risedronate, and etidronate is more effective than shorter treatment duration. For most therapies there was a maximum of four studies in each category, with the exception of alendronate 10 mg/day po, and as a result this is the only product for which results were reasonably comparable with respect to trial duration.

Most of the trials included in this NMA were secondary prevention trials and as a result were postmenopausal women with more severe osteoporotic disease as assessed by

previous fracture or decreased BMD. Because of the smaller number of primary prevention studies, not all analyses could be performed for each outcome.

Observational studies investigating bisphosphonates have been performed looking at fracture outcomes and adverse events. Network meta-analysis does offer the potential to include observational studies in the analysis, but this would have created more heterogeneity in the study and the strength of manintaing randomization would have been lost, so this was not done. Not including this information however is a study limitation.

Finally, although the analyses of total withdrawals and adverse event withdrawals did not reveal any statistically significant differences among the bisphosphonates, the lack of information concerning specific adverse events limits any conclusions about potential differences among the bisphosphonates from a safety perspective. This is frequently a challenge when evaluating results from published RCTs, which are not powered to evaluate specific adverse events.

5.4.3 Conclusions

Overall, zoledronic acid and alendronate were found to be the most effective bisphosphonates for fracture prevention in osteoporotic women. Although this study focused on osteoporosis in postmenopausal women, this is a growing concern in older men as well, and these results can be generalized to the wider population. These therapies appear to perform better for secondary prevention compared with primary prevention, and when treatment is longer than 3 years. The optimal length of therapy with bisphosphonates remains a question of debate and this is an area that should be explored in future research as the population eligible for treatment with these therapies will continue to grow. No differences were found in withdrawals from clinical trials amongst the different bisphosphonates. Analysis of specific adverse events would be helpful in determining if there is a difference in the benefit-harm profile of the different bisphosphonates, and will assist in making individual treatment choices by patients with their health care professionals.

CHAPTER 6 CONCLUDING REMARKS

Network meta-analysis is a type of indirect treatment comparison that is becoming more widely used to compare different interventions by clinicians, health technology assessors and guideline developers[175]. It is especially useful given that many direct treatment comparisons are not conducted, and are unlikely to be performed. Medical journals are now providing guidance to practitioners on how to appraise and interpret publications that are based on these methodologies[176].

The analyses presented in this thesis evaluating the effectiveness of bisphosphonates in fracture prevention in osteoporosis are for the most part consistent with previous reports. Although each study used slightly different methodologies and inclusion criteria, the overall agreement does support the robustness of NMA as a technique for conducting indirect treatment comparisons as results are reproducible. These types of analyses can be helpful to both policy makers and clinicians while comparing products in the same and different therapeutic classes so as to make recommendations for populations or specific individuals.

This study examined proxy measures of safety through the outcomes of total and adverse event withdrawals and did not find any differences between the agents studied, however, the lack of long-term follow-up in RCTs and minimal adverse event reporting limit the conclusions that can be made. The optimal length of therapy with these agents is still a matter of debate, and the long-term consequences are unknown, although concerns have been raised with respect to osteonecrosis of the jaw, and atypical fractures. As bisphosphonates are therapies that are used for many years, observational studies are likely the most feasible mechanism by which to determine if there are any significant safety differences between the individual bisphosphonates, which will likely continue to be widely used in osteoporosis.

REFERENCES

1. Leboime A, Confavreux CB, Mehsen N, Paccou J, David C, Roux C. Osteoporosis and mortality. Joint Bone Spine 2010 Dec;77 Suppl 2:S107-12.
2. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet 2011 Apr 9;377(9773):1276-1287.
3. Papadimitropoulos EA, Coyte PC, Josse RG, Greenwood CE. Current and projected rates of hip fracture in Canada. CMAJ 1997 Nov 15;157(10):1357-1363.
4. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. Arch Intern Med 1991 Oct;151(10):2026-2032.
5. Fleisch H, Russell RG, Straumann F. Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. Nature 1966 Nov 26;212(5065):901-903.
6. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. Bone 1999 Jul;25(1):97-106.
7. Russell RG. Bisphosphonates: the first 40 years. Bone 2011 Jul;49(1):2-19.
8. Bianchi G, Sambrook P. Oral nitrogen-containing bisphosphonates: a systematic review of randomized clinical trials and vertebral fractures. Curr Med Res Opin 2008 Sep;24(9):2669-2677.
9. European Medicines Agency. Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis. 2005:1-10. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003405.pdf
10. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Int Med 2008;148(3):197-213.
11. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008 Jan 23;(1)(1):CD001155.
12. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008 Jan 23;(1)(1):CD003376.
13. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008 Jan 23;(1)(1):CD004523.
14. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement 2000 March 27-29; 17(1): 1–45.
15. Warriner AH, Saag KG. Osteoporosis diagnosis and medical treatment. Orthop Clin North Am 2013 Apr;44(2):125-135.
16. Hodsman AB, Hanley DA, Josse R. Do bisphosphonates reduce the risk of osteoporotic fractures? An evaluation of the evidence to date. CMAJ 2002 May 28;166(11):1426-1430.
17. Compston J. Osteoporosis: social and economic impact. Radiol Clin North Am 2010 May;48(3):477-482.

18. Hanley DA, Josse RG. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. 1. Introduction. CMAJ 1996 Oct 1;155(7):921-923.
19. Brown JP, Josse RG, Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002 Nov 12;167(10 Suppl):S1-34.
20. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO study group. World Health Organ Tech Rep Ser 1994;843:1-129.
21. Armas LA, Recker RR. Pathophysiology of osteoporosis: new mechanistic insights. Endocrinol Metab Clin North Am 2012 Sep;41(3):475-486.
22. Statistics Canada. A Portrait of Seniors in Canada. 2007. Available from: http://www.statcan.gc.ca/pub/89-519-x/89-519-x2006001-eng.pdf 2007.
23. National Osteoporosis Foundation. America's bone health: The state of osteoporosis and low bone mass in our nation. 2002.
24. Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The assessment of fracture risk. J Bone Joint Surg Am 2010 Mar;92(3):743-753.
25. Vestergaard P, Rejnmark L, Mosekilde L. Osteoporosis is markedly underdiagnosed: a nationwide study from Denmark. Osteoporos Int 2005 Feb;16(2):134-141.
26. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993 Jan 9;341(8837):72-75.
27. Carmona R. Bone health and osteoporosis. A report of the Surgeon General. Rockville, MD: US Department of Health and Human Services. 2004.
28. Bessette L, Ste-Marie LG, Jean S, Davison KS, Beaulieu M, Baranci M, et al. The care gap in diagnosis and treatment of women with a fragility fracture. Osteoporos Int 2008 Jan;19(1):79-86.
29. Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton LJ,3rd. Classification of vertebral fractures. J Bone Miner Res 1991 Mar;6(3):207-215.
30. Guggenbuhl P. Osteoporosis in males and females: Is there really a difference? Joint Bone Spine 2009 Dec;76(6):595-601.
31. Ioannidis G, Papaioannou A, Hopman WM, Akhtar-Danesh N, Anastassiades T, Pickard L, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ 2009 Sep 1;181(5):265-271.
32. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999 Mar 13;353(9156):878-882.
33. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009 Feb 4;301(5):513-521.
34. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1999 May;14(5):821-828.

35. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007 Mar;22(3):465-475.
36. Tarride J-E, Hopkins R, Leslie WD, Morin S, Bischof M, Goeree R. The economic burden of acute care hospitalizations for fractures related to osteoporosis in Canada. Med Decis Making 2011;21(1):E87.
37. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008 Sep;83(9):1032-1045.
38. Heaney RP, Recker RR, Saville PD. Nutrition classics. The Journal of Laboratory and Clinical Medicine, Volume 92, 1978: Menopausal changes in calcium balance performance. Nutr Rev 1983 Mar;41(3):86-89.
39. Recker R, Lappe J, Davies K, Heaney R. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res 2000 Oct;15(10):1965-1973.
40. Fleisch H, Bisaz S. Isolation from urine of pyrophosphate, a calcification inhibitor. Am J Physiol 1962 Oct;203:671-675.
41. Fleisch H, Russell RG, Francis MD. Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. Science 1969 Sep 19;165(3899):1262-1264.
42. Russell RG, Muhlbauer RC, Bisaz S, Williams DA, Fleisch H. The influence of pyrophosphate, condensed phosphates, phosphonates and other phosphate compounds on the dissolution of hydroxyapatite in vitro and on bone resorption induced by parathyroid hormone in tissue culture and in thyroparathyroidectomised rats. Calcif Tissue Res 1970;6(3):183-196.
43. Diab DL, Watts NB. Bisphosphonates in the treatment of osteoporosis. Endocrinol Metab Clin North Am 2012 Sep;41(3):487-506.
44. Smith R, Russell RG, Bishop M. Diphosphonates and Page's disease of bone. Lancet 1971 May 8;1(7706):945-947.
45. Bassett CA, Donath A, Macagno F, Preisig R, Fleisch H, Francis MD. Diphosphonates in the treatment of myositis ossificans. Lancet 1969 Oct 18;2(7625):845.
46. Roelofs AJ, Thompson K, Ebetino FH, Rogers MJ, Coxon FP. Bisphosphonates: molecular mechanisms of action and effects on bone cells, monocytes and macrophages. Curr Pharm Des 2010;16(27):2950-2960.
47. Nussbaum SR, Warrell RP,Jr, Rude R, Glusman J, Bilezikian JP, Stewart AF, et al. Dose-response study of alendronate sodium for the treatment of cancer-associated hypercalcemia. J Clin Oncol 1993 Aug;11(8):1618-1623.
48. Body JJ, Lortholary A, Romieu G, Vigneron AM, Ford J. A dose-finding study of zoledronate in hypercalcemic cancer patients. J Bone Miner Res 1999 Sep;14(9):1557-1561.
49. Ralston SH, Thiebaud D, Herrmann Z, Steinhauer EU, Thurlimann B, Walls J, et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. Br J Cancer 1997;75(2):295-300.
50. Frith JC, Monkkonen J, Auriola S, Monkkonen H, Rogers MJ. The molecular mechanism of action of the antiresorptive and antiinflammatory drug clodronate: evidence for the formation in vivo of a metabolite that inhibits bone resorption and

causes osteoclast and macrophage apoptosis. Arthritis Rheum 2001 Sep;44(9):2201-2210.
51. Lehenkari PP, Kellinsalmi M, Napankangas JP, Ylitalo KV, Monkkonen J, Rogers MJ, et al. Further insight into mechanism of action of clodronate: inhibition of mitochondrial ADP/ATP translocase by a nonhydrolyzable, adenine-containing metabolite. Mol Pharmacol 2002 May;61(5):1255-1262.
52. Luckman SP, Hughes DE, Coxon FP, Graham R, Russell G, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. J Bone Miner Res 1998 Apr;13(4):581-589.
53. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008 Jun;19(6):733-759.
54. Kubo T, Shimose S, Matsuo T, Fujimori J, Ochi M. Minodronate for the treatment of osteoporosis. Drugs Today (Barc) 2010 Jan;46(1):33-37.
55. Boonen S, Laan RF, Barton IP, Watts NB. Effect of osteoporosis treatments on risk of non-vertebral fractures: Review and meta-analysis of intention-to-treat studies. 2005;16 (10):1291-1298.
56. Heaney RP, Saville PD. Etidronate disodium in postmenopausal osteoporosis. Clin Pharmacol Ther 1976 Nov;20(5):593-604.
57. Health Canada. Notice of Compliance (NOC) Database. 2012; Available from: http://webprod3.hc-sc.gc.ca/noc-ac/index-eng.jsp. Accessed January 30, 2012.
58. Food and Drug Administration. Drugs@FDA, FDA Approved Drug Products. 2012; Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=BONIVA. Accessed January 30, 2012.
59. European Medicines Agency. European public assessment reports. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000502/human_med_000677.jsp&mid=WC0b01ac058001d124. Accessed January 30, 2012.
60. Rizzoli R. Bisphosphonates for post-menopausal osteoporosis: are they all the same? Q J Med 2011;104(4):281-300.
61. Galesanu C, Lisnic N, Mocanu V, Florescu A, Loghin AI, Galesanu MR. Efficacy of bisphosphonates in the treatment of postmenopausal osteoporosis. 2011;Conference: IOF Regionals - 1st Middle-East and Africa Osteoporosis Meeting Dubai United Arab Emirates. Conference Publication: 22:S739.
62. Miller PD, Epstein S, Sedarati F, Reginster JY. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. Curr Med Res Opin 2008 Jan;24(1):207-213.
63. Vilario SIA, Vilario C, Schwartz A, Contreras Ortiz O, Dotto J. Comparison of different treatments on postmenopausal patients (POSTM). 2009;Conference: 8th European Congress on Menopause, EMAS London United Kingdom. Conference Publication: (var.pagings). 63:S95.
64. Kushida K, Fukunaga M, Kishimoto H, Shiraki M, Itabashi A, Inoue T, et al. A comparison of incidences of vertebral fracture in Japanese patients with involutional

osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. J Bone Miner Metab 2004;22(5):469-478.
65. Ringe JD, Doherty JG. Absolute risk reduction in osteoporosis: assessing treatment efficacy by number needed to treat. Rheumatol Int 2010 May;30(7):863-869.
66. McClung M, Harris ST, Miller PD, Bauer DC, Davison KS, Dian L, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med 2013 Jan;126(1):13-20.
67. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997 Jun;50(6):683-691.
68. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004 Oct 30;23(20):3105-3124.
69. Jansen JP, Bergman GJ, Huels J, Olson M. The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-nonhip fractures in osteoporosis: a network meta-analysis. Semin Arthritis Rheum 2011 Feb;40(4):275-84.e1-2.
70. Hopkins RB, Goeree R, Pullenayegum E, Adachi JD, Papaioannou A, Xie F, et al. The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Musculo Dis 2011;12(209).
71. Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int 2013 Jan;24(1):209-217.
72. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010 Apr;95(4):1555-1565.
73. Health Canada. Product monographs, alendronate. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
74. Health Canada. Product monographs, etidronate. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
75. Health Canada. Product monographs, risedronate. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
76. Health Canada. Product monographs, zoledronic acid. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
77. Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLoS Med 2011 May;8(5):e1001026.
78. Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ 2006 Feb 28;174(5):645-646.
79. Mittmann N, Liu BA, Knowles SR, Shear NH. Meta-analysis and adverse drug reactions. CMAJ 1999 Apr 6;160(7):987-988.
80. Ioannidis JP, Mulrow CD, Goodman SN. Adverse events: the more you search, the more you find. Ann Intern Med 2006 Feb 21;144(4):298-300.
81. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Eng J Med 2011 May 5;364(18):1728-1737.

82. Saleh A, Hegde VV, Potty AG, Lane JM. Bisphosphonate therapy and atypical fractures. Orthop Clin North Am 2013 Apr;44(2):137-151.
83. Health Canada. Product monographs, raloxifene. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
84. Health Canada. Product monographs, teriparatide. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
85. Health Canada. Product monographs,denusomab. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng. Accessed March 19, 2014.
86. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 1992 Jul 8;268(2):240-248.
87. Oxman AD, Guyatt GH. The science of reviewing research. Ann N Y Acad Sci 1993 Dec 31;703:125-33; discussion 133-4.
88. Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochracne-handbook.org.
89. Moher D, Stewart L, Shekelle P. Establishing a new journal for systematic review products. Syst Rev 2012 Feb 9;1:1-4053-1-1.
90. Glass G. Primary, secondary and meta-analysis of research. Educational Researcher 1976;5(10):3-8.
91. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002 Jun 15;21(11):1539-1558.
92. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-560.
93. Adami S, Felsenberg D, Christiansen C, Robinson J, Lorenc RS, Mahoney P, et al. Efficacy and safety of ibandronate given by intravenous injection once every 3 months. Bone 2004;34(5):881-889.
94. Bala Y, Barr CE, Boivin G. Daily and intermittent oral ibandronate improve bone tissue hardness and maintained its mineralization. 2010;Conference: IOF World Congress on Osteoporosis and 10th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, IOF WCO - ECCEO 10 Florence Italy. Conference Start: 20100505 Conference End: 20100508. Conference Pub:S155.
95. Binkley N, Silverman SL, Simonelli C, Santiago N, Kohles JD, Dasic G, et al. Monthly ibandronate suppresses serum CTX-I within 3 days and maintains a monthly fluctuating pattern of suppression. Osteoporos Int2009;20(9):1595-1601.
96. Borst H, Bock O, Beller G, Kratzsch M, Degner C, Profittlich H, et al. Effects of monthly oral ibandronate 150 MG on BV/TV and trabecular separation measured in vivo by micro-CT at the distal tibia in postmenopausal women with osteoporosis or osteopenia. 2010: IOF World Congress on Osteoporosis and 10th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, IOF WCO - ECCEO 10 Florence Italy. Osteoporos Int 2010;21(Suppl 1):S164.
97. Chapurlat R, Laroche M, Thomas T, Rouanet S, Delmas PD, De Vernejoul MC. Effect of oral ibandronate on bone microarchitecture in women with osteopenia a randomized placebo-controlled trial. 2010;Conference: American College of

Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 10 Philadelphia, PA United States.
98. Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, et al. Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. Curr Med Opin 2005;21(3):391-401.
99. Cooper C, Emkey RD, McDonald RH, Hawker G, Bianchi G, Wilson K, et al. Efficacy and safety of oral weekly ibandronate in the treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2003;88(10):4609-4615.
100. Delmas PD, Recker RR, Chesnut CH,3rd, Skag A, Stakkestad JA, Emkey R, et al. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. Osteoporos Int 2004;15(10):792-798.
101. Duraj V, Backa T, Rapushi E, Zoto A, Roshi E. The efficiency of Bonviva (Ibandronate) in women with pre-post menopause. Med Arh 2010;64(4):225-227.
102. Emkey R, Delmas PD, Bolognese M, Borges JLC, Cosman F, Ragi-Eis S, et al. Efficacy and tolerability of once-monthly oral ibandronate (150 mg) and once-weekly oral alendronate (70 mg): additional results from the Monthly Oral Therapy With Ibandronate For Osteoporosis Intervention (MOTION) study. Clin Ther 2009;31(4):751-761.
103. Engelke K, Fuerst T, Dasic G, Davies RY, Genant HK. Regional distribution of spine and hip QCT BMD responses after one year of once-monthly ibandronate in postmenopausal osteoporosis. Bone 2010;46(6):1626-1632.
104. Felsenberg D, Miller P, Armbrecht G, Wilson K, Schimmer RC, Papapoulos SE. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. Bone 2005;37(5):651-654.
105. Genant HK, Fuerst T, Engelke K, Davies RY, Dasic G. Effect of once-monthly oral ibandronate On hip cortical and sub-cortical quantitative computed tomography (QCT) parameters in postmenopausal osteoporosis. 2009;Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 09 Atlanta, GA United States. Conference Publication: 60:866.
106. Harris ST, Reginster JY, Harley C, Blumentals WA, Poston SA, Barr CE, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study. Bone 2009;44(5):758-765.
107. Lewiecki EM, Keaveny TM, Kopperdahl DL, Genant HK, Engelke K, Fuerst T, et al. Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis. J Clin Endrocrinol Metab 2009;94(1):171-180.
108. McClung MR, Wasnich RD, Recker R, Cauley JA, Chesnut CH,3rd, Ensrud KE, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. J Bone Miner Res 2004;19(1):11-18.
109. Ravn P, Clemmesen B, Riis BJ, Christiansen C. The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and

treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind, placebo-controlled dose-finding study. Bone 1996 Nov;19(5):527-533.
110. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study.[Erratum appears in Ann Rheum Dis. 2008 Feb;67(2):280]. Ann Rheum Dis 2006;65(5):654-661.
111. Riis BJ, Ise J, von Stein T, Bagger Y, Christiansen C. Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. J Bone Miner Res 2001;16(10):1871-1878.
112. Sambrook P, Cranney A, Adachi JD. Risk reduction of non-vertebral fractures with intravenous ibandronate: post-hoc analysis from DIVA. Curr Med Opin Res 2010;26(3):599-604.
113. Stakkestad JA, Benevolenskaya LI, Stepan JJ, Skag A, Nordby A, Oefjord E, et al. Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. Ann Rheum Dis 2003;62(10):969-975.
114. Stakkestad JA, Lakatos P, Lorenc R, Sedarati F, Neate C, Reginster J. Monthly oral ibandronate is effective and well tolerated after 3 years: the MOBILE long-term extension. Clin Rheum 2008;27(8):955-960.
115. Tanko LB, Felsenberg D, Czerwinski E, Burdeska A, Jonkanski I, Hughes C, et al. Oral weekly ibandronate prevents bone loss in postmenopausal women. Bone 2003;254(2):159-167.
116. Tanko LB, Mouritzen U, Lehmann HJ, Warming L, Moelgaard A, Christgau S, et al. Oral ibandronate: changes in markers of bone turnover during adequately dosed continuous and weekly therapy and during different suboptimally dosed treatment regimens. J Int Med 2003;32(6):687-693.
117. Thiebaud D, Burckhardt P, Kriegbaum H, Huss H, Mulder H, Juttmann JR, et al. Three monthly intravenous injections of ibandronate in the treatment of postmenopausal osteoporosis. Am J Med 1997;103(4):298-307.
118. Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19(8):1241-1249.
119. Recker R, Stakkestad JA, Chesnut CH,3rd, Christiansen C, Skag A, Hoiseth A, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone 2004;34(5):890-899.
120. McClung MR, Bolognese MA, Sedarati F, Recker RR, Miller PD. Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss. Bone 2009 Mar;44(3):418-422.
121. Li M, Xing X, Zhang Z, Liu J, Zhang Z, Liu D, et al. Infusion of ibandronate once every 3 months effectively decreases bone resorption markers and increases bone mineral density in Chinese postmenopausal osteoporotic women: a 1-year study. J Bone Miner Res 2010;28(3):299-305.
122. Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, et al. Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Osteoporos Int 2009 Feb; 20(2):291-297.

123. Bachmann G, Kriegman A, Goncalves J, Kianifard F, Warren M, Simon JA. Effect of zoledronic acid compared with raloxifene on bone turnover markers in postmenopausal women with low bone density. Menopause 2011;18(8):851-856.
124. Boonen S, Black DM, Colon-Emeric CS, Eastell R, Magaziner JS, Eriksen EF, et al. Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. J Am Geriatr Soc 2010 Feb;58(2):292-299.
125. Boonen S, Orwoll E, Magaziner J, Colon-Emeric CS, Adachi JD, Bucci-Rechtweg C, et al. Once-yearly zoledronic acid in older men compared with women with recent hip fracture. 2011;59(11):2084-2090.
126. Devogelaer JP, Brown JP, Burckhardt P, Meunier PJ, Goemaere S, Lippuner K, et al. Zoledronic acid efficacy and safety over five years in postmenopausal osteoporosis. Osteoporos Int 2007 Sep;18(9):1211-1218.
127. Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR. The antiresorptive effects of a single dose of zoledronate persist for two years: A randomized, placebo-controlled trial in osteopenic postmenopausal women. J Clin Endocrinol Metab 2009;64(7):462-463.
128. Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR. The antiresorptive effects of a single dose of zoledronate persist for two years: a randomized, placebo-controlled trial in osteopenic postmenopausal women. J Clin Endocrinol Metab 2009 Feb;94(2):538-544.
129. Grey A, Bolland M, Wattie D, Horne A, Gamble G, Reid IR. Prolonged antiresorptive activity of zoledronate: A randomized, controlled trial. J Bone Miner Res 2010;25(10):2251-2255.
130. Hwang JS, Chin LS, Chen JF, Yang TS, Chen PQ, Tsai KS, et al. The effects of intravenous zoledronic acid in Chinese women with postmenopausal osteoporosis. J Bone Miner Res 2011(3):328-333.
131. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007 Nov 1;357(18):1799-1809.
132. McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone 2007(1):122-128.
133. McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL. Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. Obstet Gynecol 2009 Nov;114(5):999-1007.
134. Reid DM, Devogelaer JP, Saag K, Keen R, Roux C, Lau CS, et al. Comparison of the efficacy and safety of a single infusion of zoledronic acid 5 mg with daily oral risedronate 5 mg in patients with glucocorticoid-induced osteoporosis: Results from a 1-year randomised, double-blind trial. N Eng J Med 2009;48:i105-i106.
135. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone 2007(5):1238-1243.

136. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007 May 3;356(18):1809-1822.
137. Grey A, Bolland M, Wong S, Horne A, Gamble G, Reid IR. Low-dose zoledronate in osteopenic postmenopausal women: A randomized controlled trial. J Clin Endocrinol Metab 2012;97(1):286-292.
138. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012 Jun;41(3):818-827.
139. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2012; available from http://www.nicedsu.org.uk
140. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996 Dec 7;348(9041):1535-1541.
141. Bone HG, Downs RW,Jr, Tucci JR, Harris ST, Weinstein RS, Licata AA, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab 1997 Jan;82(1):265-274.
142. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998 Dec 23-30;280(24):2077-2082.
143. Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract 2001 Oct;55(8):505-509.
144. Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab 2000 May;85(5):1895-1900.
145. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999 Oct 13;282(14):1344-1352.
146. Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric 2005 Sep;8(3):251-262.
147. Lyritis GP, Tsakalakos N, Paspati I, Skarantavos G, Galanos A, Androulakis C. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. Clin Rheumatol 1997 Jun;16(4):354-360.
148. Meunier PJ, Confavreux E, Tupinon I, Hardouin C, Delmas PD, Balena R. Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year follow-up). J Clin Endocrinol Metab 1997 Sep;82(9):2784-2791.

149. Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker K. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporos Int 1997;7(1):52-58.
150. Pouilles JM, Tremollieres F, Roux C, Sebert JL, Alexandre C, Goldberg D, et al. Effects of cyclical etidronate therapy on bone loss in early postmenopausal women who are not undergoing hormonal replacement therapy. Osteoporos Int 1997;7(3):213-218.
151. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11(1):83-91.
152. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990 Jul 12;323(2):73-79.
153. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 1998 Mar;104(3):219-226.
154. Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. N Engl J Med 1998 Feb 19;338(8):485-492.
155. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. Am J Med 2004 Oct 15;117(8):549-555.
156. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001 Feb 1;344(5):333-340.
157. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9(5):461-468.
158. Qin L, Choy W, Au S, Fan M, Leung P. Alendronate increases BMD at appendicular and axial skeletons in patients with established osteoporosis. J Orthop Surg Res 2007 May 21;2:9.
159. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990 May 3;322(18):1265-1271.
160. Valimaki MJ, Farrerons-Minguella J, Halse J, Kroger H, Maroni M, Mulder H, et al. Effects of risedronate 5 mg/d on bone mineral density and bone turnover markers in late-postmenopausal women with osteopenia: a multinational, 24-month, randomized, double-blind, placebo-controlled, parallel-group, phase III trial. Clin Ther 2007 Sep;29(9):1937-1949.
161. Yan Y, Wang W, Zhu H, Li M, Liu J, Luo B, et al. The efficacy and tolerability of once-weekly alendronate 70 mg on bone mineral density and bone turnover markers

in postmenopausal Chinese women with osteoporosis. J Bone Miner Metab 2009;27(4):471-478.
162. Fitzpatrick LA, Dabrowski CE, Cicconetti G, Gordon DN, Papapoulos S, Bone III HG, and Bilezikian JP. The effects of ronacaleret, a calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab 2011 Aug;96(8):2441-2449.
163. Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. J Bone Miner Res 1998 Sep;13(9):1431-1438.
164. Greenspan S, Field-Munves E, Tonino R, Smith M, Petruschke R, Wang L, et al. Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. Mayo Clin Proc 2002 Oct;77(10):1044-1052.
165. Ascott-Evans BH, Guanabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med 2003 Apr 14;163(7):789-794.
166. Herd RJ, Balena R, Blake GM, Ryan PJ, Fogelman I. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. Am J Med 1997 Aug;103(2):92-99.
167. Kung AW, Yeung SS, Chu LW. The efficacy and tolerability of alendronate in postmenopausal osteoporotic Chinese women: a randomized placebo-controlled study. Calcif Tissue Int 2000 Oct;67(4):286-290.
168. Li Y, Zhang Z, Deng X, Chen, L. Efficacy and safety of risedronate sodium in treatment of postmenopausal osteoporosis. J Huazhong Univ Sci Technolog Med Sci 2005;25(5):527-529.
169. Chesnut CH,3rd, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. Am J Med 1995 Aug;99(2):144-152.
170. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int 1997;7(5):488-495.
171. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995 Nov 30;333(22):1437-1443.
172. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC,Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab 1998 Feb;83(2):396-402.
173. Pacifici R, McMurtry C, Vered I, Rupich R, Avioli LV. Coherence therapy does not prevent axial bone loss in osteoporotic women: a preliminary comparative study. J Clin Endocrinol Metab 1988 Apr;66(4):747-753.
174. Shiota E, Tsuchiya K, Yamaoka K, Kawano O. Effect of intermittent cyclical treatment with etidronate disodium (HEBP) and calcium plus alphacalcidol in postmenopausal osteoporosis. J Orthop Sci 2001;6(2):133-136.

175. Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics 2008;26(9):753-767.
176. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ 2013 May 14;346:f2914.

APPENDIX 1 SEARCH STRATEGY FOR IBANDRONATE RCTS

Databases: CENTRAL, DARE, HTA Datbase and NHS EED, The Cochrane Library, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to 2011>; EMBASE <1980 to 2011>; Scopus

1. osteoporosis, postmenopausal/
2. osteoporosis/
3. osteoporosis.tw.
4. exp bone density/
5. bone loss$.tw.
6. (bone adj2 densit$).tw.
7. or/2-6
8. menopause
9. post-menopaus$.tw.
10. postmenopaus$.tw.
11. or/8-10
12. 7 and 11
13. 1 or 12
14. ibandronate/
15. ibandronate.tw,rn.
16. boniva.tw.
17. bondenza.tw.
18. or/14-17
19. 13 and 18
20. meta-analysis.pt.sh
21. (meta-anal: or metaanal:).tw.
22. (quantitativ: review: or quantitativ: overview:).tw.
23. (methodologic: review: or methodologic: overview:).tw.
24. (systematic: review: or systematic: overview:).tw.
25. review.pt. and medline.tw.
26. or/20-25
27. 19 and 26
28. clinical trial.pt
29. randomized controlled trial.pt
30. tu.fs
31. dt.fs
32. random$.tw.
33. (double adj blind$).tw.
34. placebo$.tw.
35. or/28-34
36. 19 and 35

APPENDIX 2 LIST OF EXCLUDED IBANDRONATE STUDIES (after full text retrieval)[63,93-117]

Study ID/First Author	Year	Reason for exclusion
Adami	2004	Lack of fracture outcome
Bala	2010	Lack of fracture outcome
Binkley	2009	Duration of therapy less than 1 year
Brst	2010	Lack of fracture outcome
Chapurlat	2010	Lack of fracture outcome
Chesnut	2005	Duplicate of another study or earlier report
Cooper	2003	Lack of an appropriate control group
Delmas	2004	Duplicate of another study or earlier report
Duraj	2010	Lack of an appropriate control group
Emkey	2009	Lack of an appropriate control group
Engelke	2010	Lack of fracture outcome
Felsenberg	2005	Duplicate of another study or earlier report
Galesanu	2011	Lack of useable fracture data
Genant	2009	Lack of fracture outcome
Harris	2009	Lack of an appropriate control group
Lewiecki	2009	Lack of fracture outcome
McClung	2004	Lack of fracture outcome
Ravn	1996	Lack of appropriate fracture data
Reginster	2006	Duration of therapy less than 1 year
Riis	2001	Lack of fracture outcome
Sambrook	2010	Lack of an appropriate control group
Stakkestad	2003	Lack of an appropriate control group
Stakkestad	2008	Lack of an appropriate control group
Tanko	2003a	Lack of an appropriate control group
Tanko	2003b	Lack of fracture outcome
Thiebaud	1997	Lack of fracture outcome
Vilario	2009	Lack of an appropriate control group

APPENDIX 3 CHARACTERISTICS OF INCLUDED IBANDRONATE STUDIES

Author and Year	Study Design	Doses used	Number in treatment and control groups	Patient Characteristics	Outcomes
Chesnut 2004[118]	Randomized controlled trial Secondary prevention Duration 3 years Blinding: Double-blind, placebo-controlled, blinded radiologists	Ibandronate 2.5 mg orally daily Ibandronate 20 mg oral every other day for 12 doses every 3 months Placebo All participants received daily Ca (500 mg) and vitamin D (400 IU)	Ibandronate 2.5 mg N = 982 Ibandronate 20 mg every other day N = 982 Placebo N= 982	Inclusion Criteria: women 55-80 years, ≥5 years postmenopausal, with one to four prevalent vertebral fractures (T4–L4) and a BMD T score of -2.0 to -5.0 in at least one vertebra (L1–L4). Exclusion Criteria: BMD T score of < -5.0 at the lumbar spine; more than two prevalent fractures of the lumbar spine; diseases, disorders, or therapy (within the last 6 months) known to affect bone metabolism; previous treatment with bisphosphonates Ibandronate 2.5 mg - mean age 69 years (SD 6), patients with 1 vertebral fracture 920 (94%) Ibandronate 20 mg every other day - mean age 69 years (SD 6), patients with 1 vertebral fracture 917 (94%) Placebo - mean age 69 (SD 6), patients with 1 vertebral fracture 906 (93%)	Vertebral and non-vertebral fractures Lateral radiographs of the thoracic and lumbar spine were performed at the screening visit to determine the presence of prevalent fractures. Lateral radiographs of the spine were performed annually for assessment of incident fractures. Fracture diagnosis was based on morphometric criteria and was further confirmed by radiologists at one of two independent central reading facilities. Clinical fractures (vertebral and non-vertebral) were identified symptomatically and reported as adverse events. Adverse events were recorded throughout the study.
McClung 2009[120]	Randomized controlled trial	Ibandronate 150 mg monthly orally	Ibandronate 150 mg monthly orally N = 77	Inclusion Criteria: ambulatory postmenopausal women aged 45–60 years with baseline mean lumbar spine (LS) BMD T-score	Fractures were a safety outcome along with other adverse events. Fractures were

	Primary prevention Duration 1 year Blinding: Double-blind, placebo-controlled, blinded radiologists	Placebo monthly orally All participants received daily Ca (500 mg) and vitamin D (400 IU)	Placebo N = 83	between −1.0 and −2.5 (L2–L4) and baseline T-score> −2.5 in 3 regions of the proximal femur: the total hip, trochanter, and femoral neck. (women with prevalent fractures were excluded) Exclusion Criteria: women with prevalent vertebral fractures, previous low-trauma osteoporotic fractures, those receiving systemic hormones, severe renal failure, diseases affecting bone metabolism, treatment with bisphosphonates in previous 2 years, history of major upper gastrointestinal disease. Ibandronate 150 mg - mean age 53.7 (SD 3.6) Placebo - mean age 53.4 (SD 3.8) Vertebral Fractures: none	confirmed by radiograph and reported as AEs. The primary endpoint was the relative change (%) from baseline in mean LS (L2–L4) BMD at 12 months of treatment, adjusted for baseline LS BMD and time since menopause, in the intent-to-treat (ITT) population. Secondary efficacy endpoints included: relative (%) change in mean BMD from baseline at the proximal femur (TH, TR, and FN) at 12 months, relative change in bone resorption marker serum C-terminal telopeptide of type 1 collagen (sCTX) from baseline at 3, 6, and 12 months, and percent responders.
Recker 2004[119]	Randomized controlled trial Secondary prevention Blinding: double-blind, placebo-	Ibandronate 0.5 mg intravenously every 3 months Ibandronate 1.0 mg intravenously Placebo intravenously every 3 months	Ibandronate 0.5 mg N = 950 Ibandronate 1.0 mg N = 961 Placebo N = 949	Inclusion criteria: postmenopausal women aged 55– 76 years, time since menopause ≥5 years, low BMD T score (-2.0 to -5.0) in at least one vertebra of the lumbar spine (L1–L4) and one to four prevalent vertebral fractures.	Vertebral and non-vertebral fractures Prevalent and incident vertebral fractures were determined using radiographs of the spine were

	controlled, blinded radiologists Duration: 3 years			Exclusion criteria: disease or disorder known to influence bone metabolism (such as Paget's disease) or had received a drug known to affect bone metabolism in the previous 6 months (such as corticosteroids, prior bisphosphonate treatment). Ibandronate 0.5 mg - mean age 67, one vertebral fracture 48% Ibandronate 1.0 mg - mean age 67, one vertebral fracture 51% Placebo - mean age 67, one vertebral fracture 50%	performed at baseline and at 12, 24 and 36 months. Adverse events were recorded throughout the study.
Li 2010[121]	Randomized controlled trial Secondary prevention Duration 1 year Blinding: Open label trial	Ibandronate 2 mg iv every 3 months Alendronate 70 mg po weekly All patients received elemental Ca (500 mg) and vitamin D3 (200 IU) daily	Ibandronate 2 mg N = 79 Alendronate 70 mg N = 79	Inclusion criteria: age between 49 and 75 years, at least 1 year postmenopausal, body mass index (BMI) 18–35 kg/m^2, T-score of lumbar spine (L2–L4) or femoral neck BMD lower than -2.0 Exclusion criteria: history of metabolic bone diseases, ovariectomy, hormone replacement therapy, treatment with bisphosphonates, calcitonin, prednisone, or heparin, or a history of serious cardiac, liver, or kidney diseases or autoimmune diseases, received an investigational new drug within the last 12 months Ibandronate 2 mg - mean age 65.6 years, previous vertebral fracture 8.9%	Fractures were a safety outcome, along with other adverse events. Primary outcomes: BMD at lumbar spine, femoral neck, and trochanter. BMD was measured at baseline and after 6 and 12 months of treatment by dual-energy X-ray absorptiometry (DXA) at the site of the right femoral neck and trochanter as well as the lumbar vertebrae (L2–L4). Secondary outcomes: total alkaline

				Alendronate 70 mg - mean age 65.1 years, previous vertebral fracture 13.9%	phosphatase (ALP) and carboxy-telopeptide cross-links of type I collagen (CTX), the change of stature after 1 year, serum calcium, phosphate, and total ALP levels
Miller 2008[62]	Randomized controlled trial Secondary prevention Duration 1 year Blinding: Double-blind, double-dummy	Ibandronate 150 mg po monthly Alendronate 70 mg po weekly All patients received vitamin D 400 IU/day and elemental calcium 500 mg/day (upper limit 1500 mg/day)	Ibandronate 150 mg N = 877 Alendronate 70 mg N = 873	Inclusion criteria: postmenopausal women aged 55–84 years, ≥ 5 years since menopause, with mean lumbar spine (L2–L4) BMD T-score < –2.5 and ≥ –5.0. Exclusion criteria: significant medical disease, inability to stand or sit upright for 60 min, hypersensitivity to bisphosphonates or to any of the excipients contained in the tablets, contraindications for calcium or vitamin D therapy, renal impairment , history of major upper gastrointestinal disease, any active disease known to influence bone metabolism, or recent treatment with drugs known to affect bone metabolism. Ibandronate 150 mg - mean age 65.6 years, previous fracture 39% Alendronate 70 mg - mean age 65.6 years, previous fracture 38.2 %	Osteoporotic fractures were an adverse event, and reported as vertebral and non-vertebral. The co-primary efficacy endpoints were the 12-month relative change (%) from baseline in mean BMD of the lumbar spine and total hip. Secondary endpoints were assessment of mean change (%) from baseline at 12 months in trochanter and femoral neck BMD

APPENDIX 4 SENSITIVITY ANALYSES FOR IBANDRONATE STUDIES

Figure 1a. Forest plot, ibandronate versus placebo, fixed effects model: Vertebral fractures.

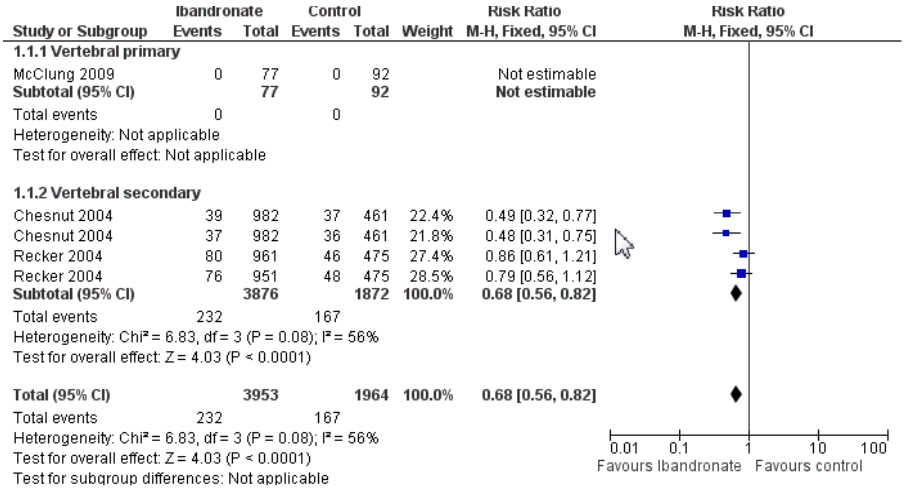


Figure 1b. Forest plot, ibandronate versus placebo, fixed effects model: Non-vertebral fractures.

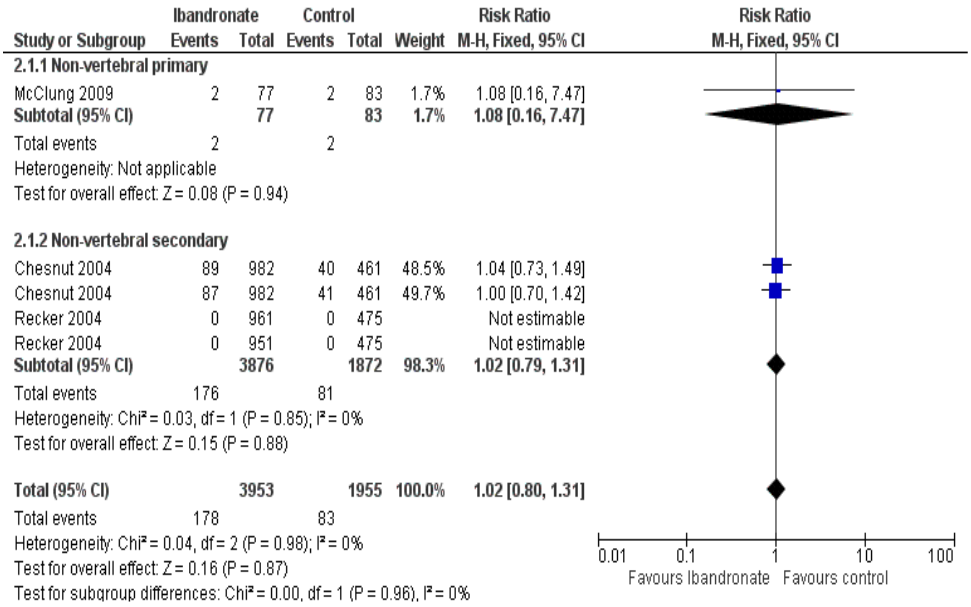


Figure 1c. Forest plot, ibandronate versus placebo, fixed effects model: Hip fractures.

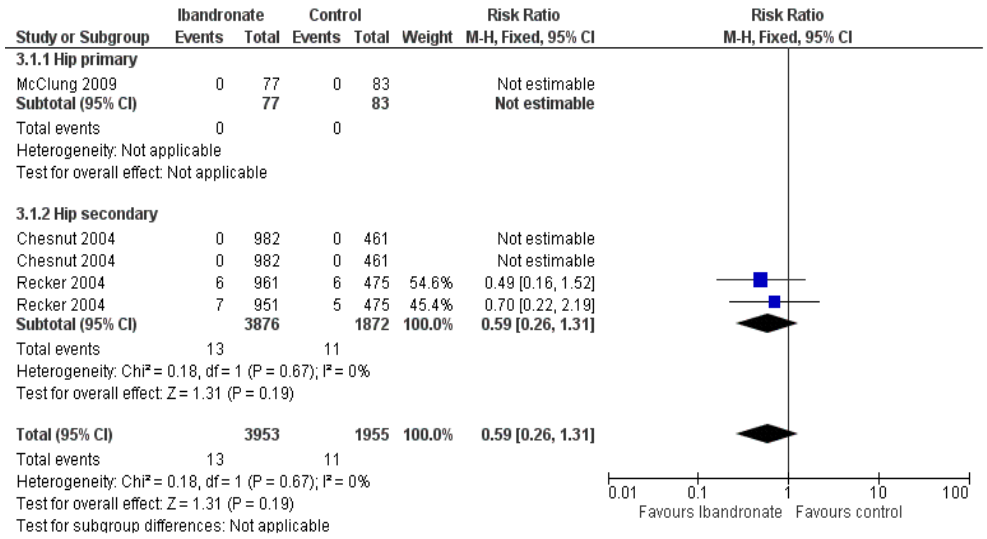


Figure 1d. Forest plot, ibandronate versus placebo, fixed effects model: Total withdrawals.

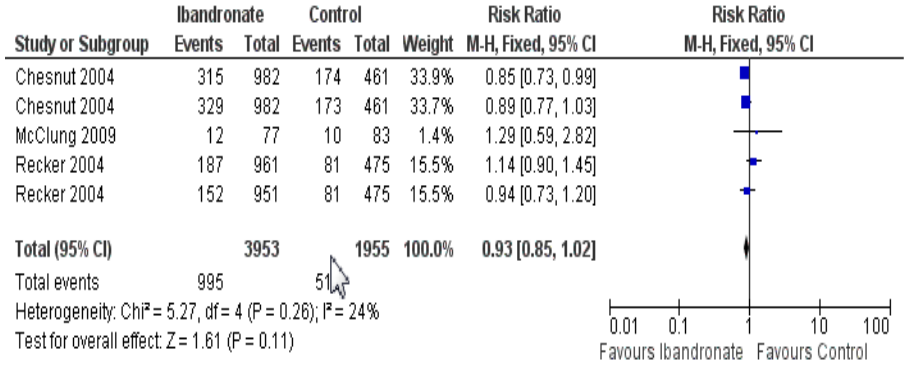


Figure 1e. Forest plot, ibandronate versus placebo, fixed effects model: Adverse event withdrawals.

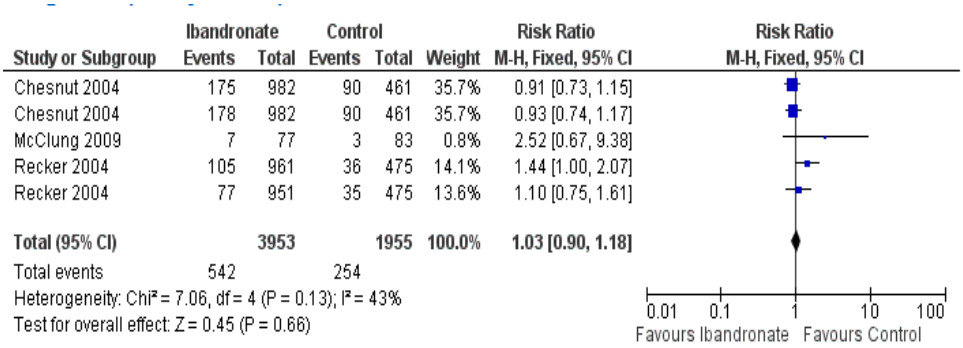


Figure 2a. Forest plot, ibandronate versus placebo, follow-up denominators: Vertebral fractures.

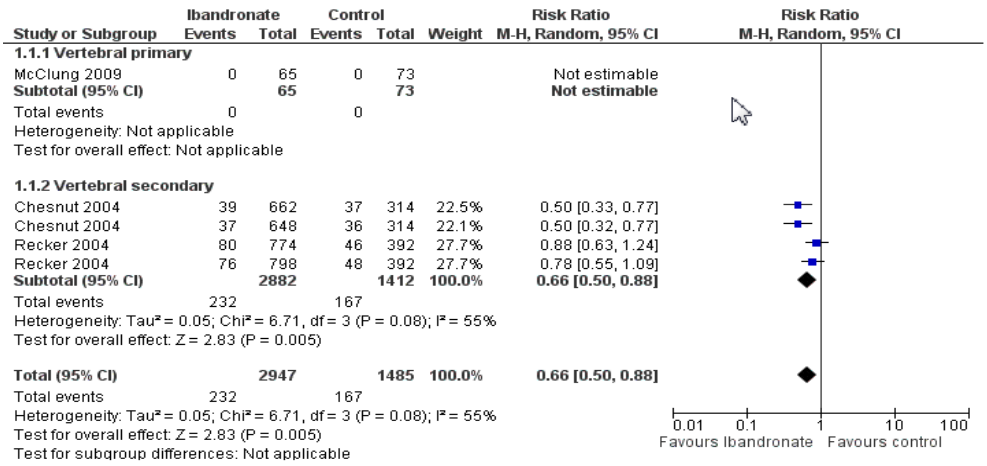


Figure 2b. Forest plot, ibandronate versus placebo, follow-up denominators: Non-vertebral fractures.

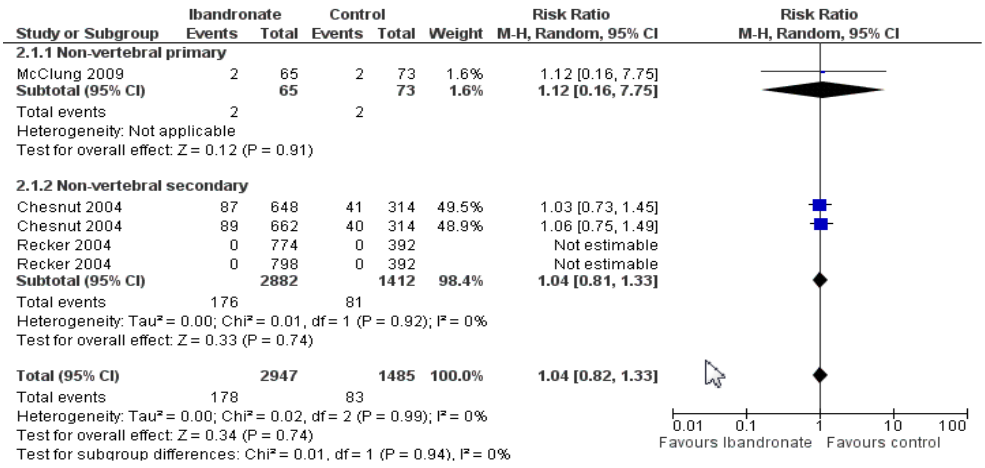


Figure 2c. Forest plot, ibandronate versus placebo, follow-up denominators: Hip fractures.

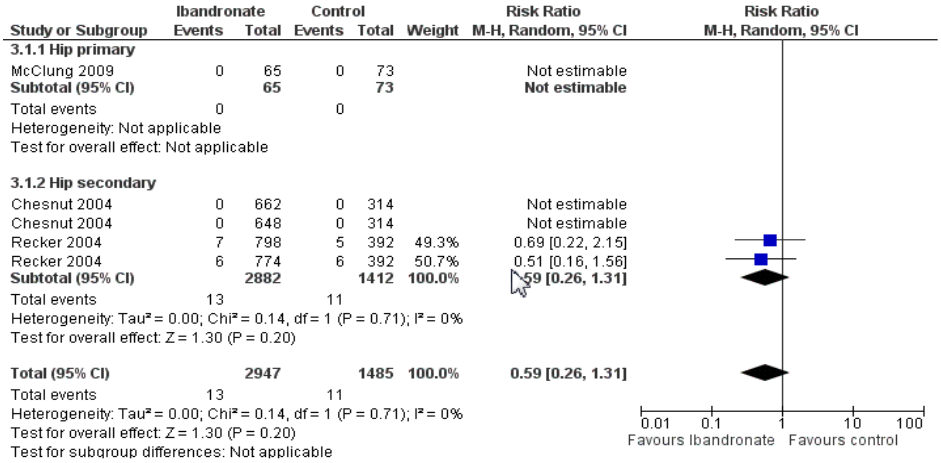


Figure 2d. Forest plot, ibandronate versus placebo, follow-up denominators: Total withdrawals.

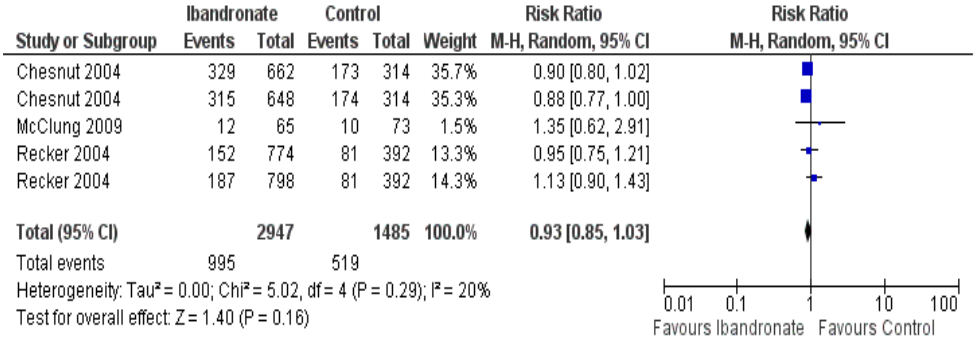


Figure 2e. Forest plot, ibandronate versus placebo, follow-up denominators: Adverse event withdrawals.

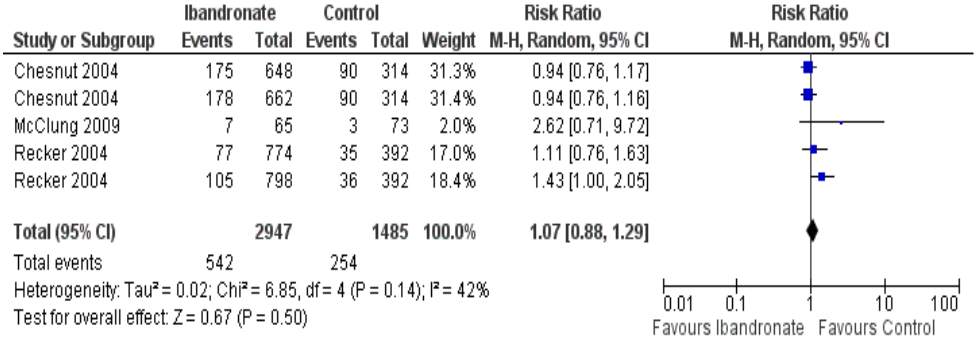


Figure 3a. Forest plot, ibandronate versus alendronate, fixed effects model: Vertebral fractures.

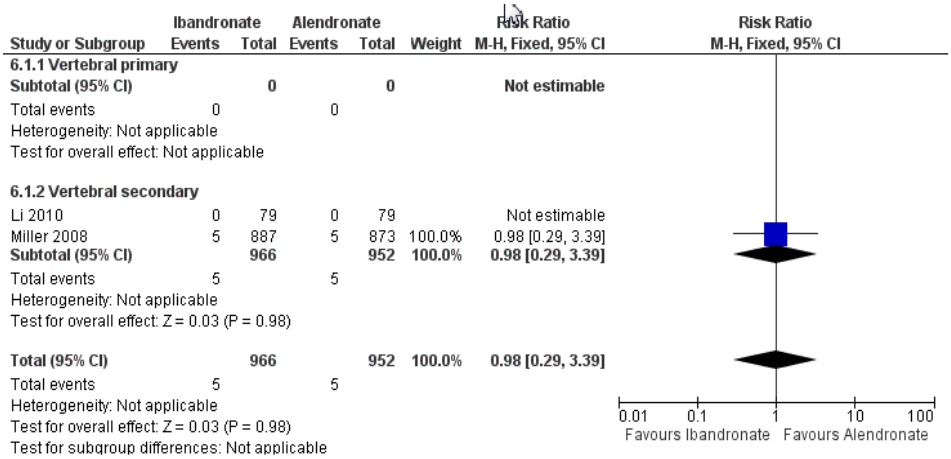


Figure 3b. Forest plot, ibandronate versus alendronate, fixed effects model: Non-vertebral fractures.

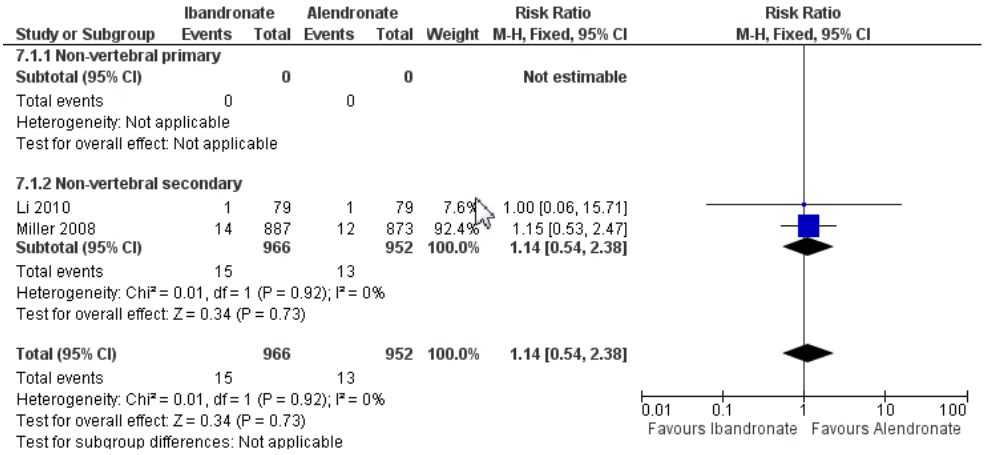


Figure 3c. Forest plot, ibandronate versus alendronate, fixed effects model: Hip fractures.

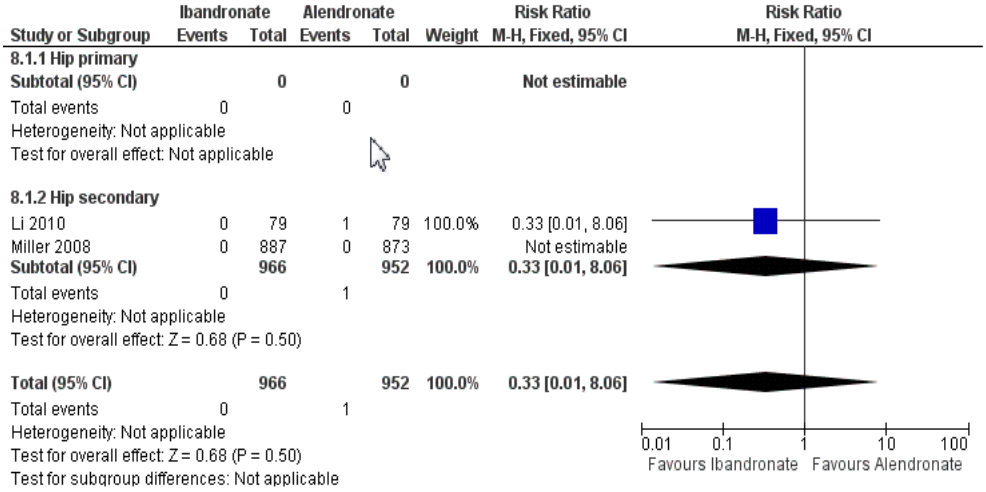


Figure 3d. Forest plot, ibandronate versus alendronate, fixed effects model: Total withdrawals.

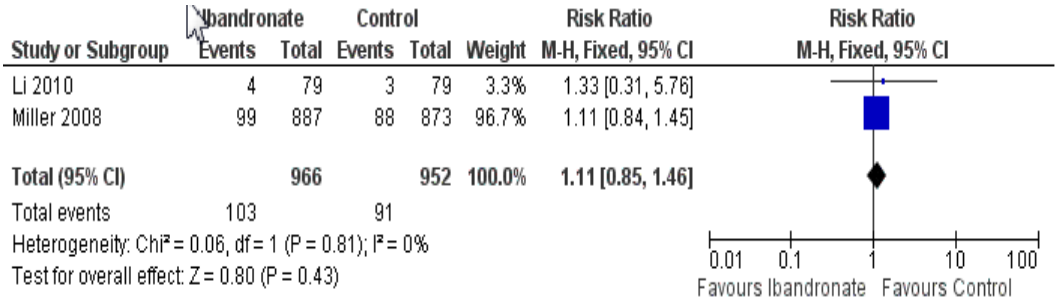


Figure 3e. Forest plot, ibandronate versus alendronate, fixed effects model: Adverse event withdrawals.

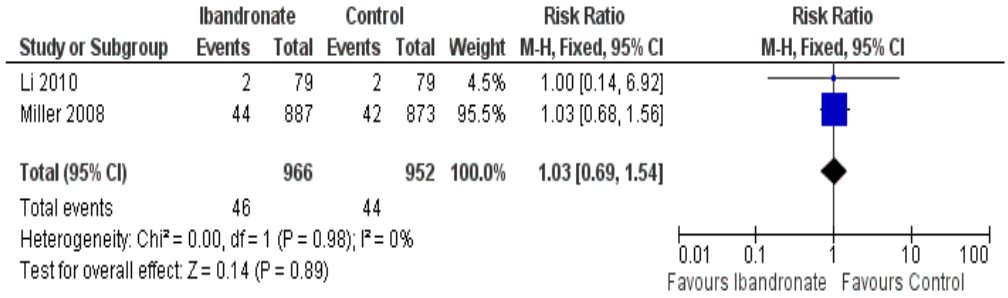


Figure 4a. Forest plot, ibandronate versus alendronate, follow-up denominators: Vertebral fractures.

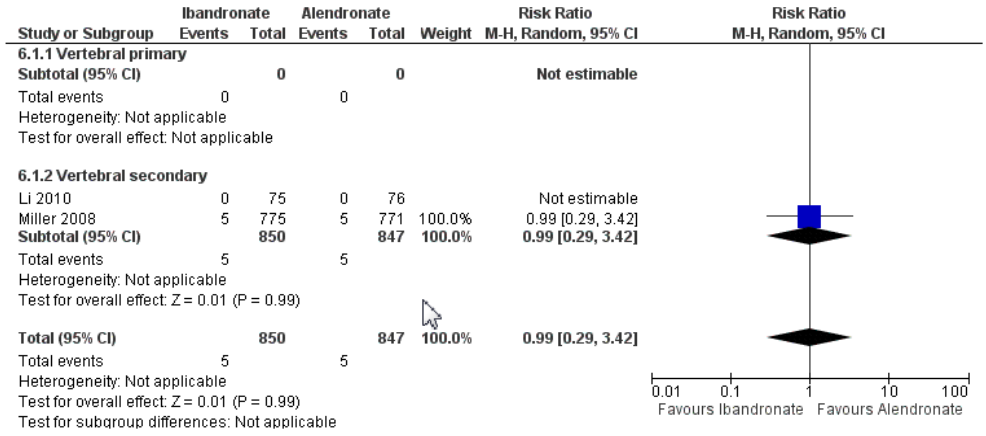


Figure 4b. Forest plot, ibandronate versus alendronate, follow-up denominators: Non-vertebral fractures.

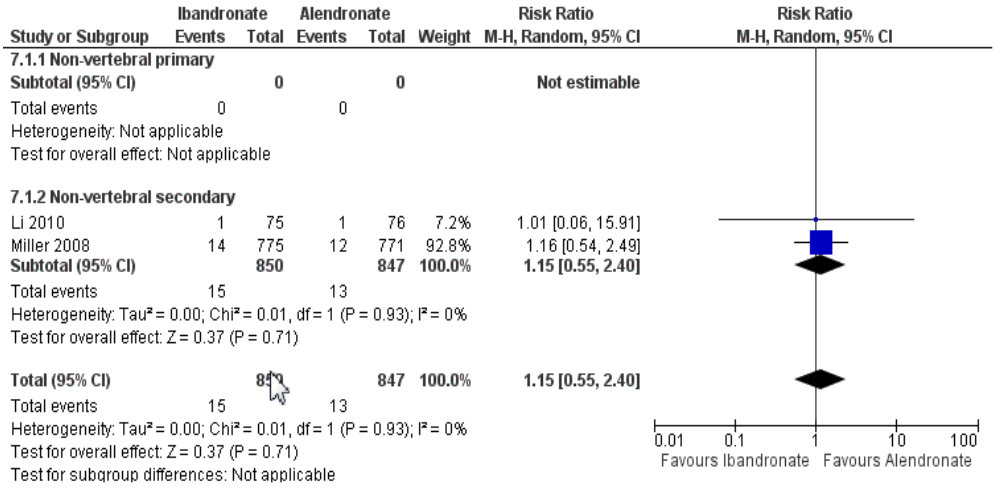


Figure 4c. Forest plot, ibandronate versus alendronate, follow-up denominators: Hip fractures.

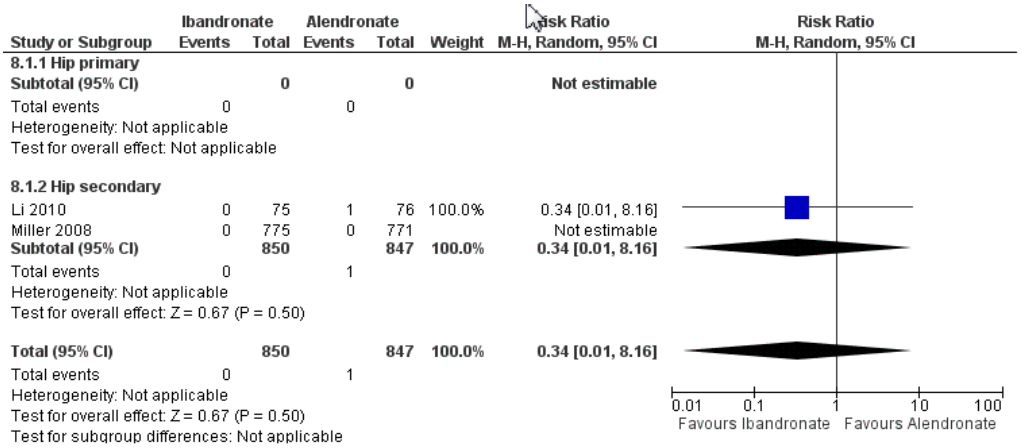


Figure 4d. Forest plot, ibandronate versus alendronate, follow-up denominators: Total withdrawals.

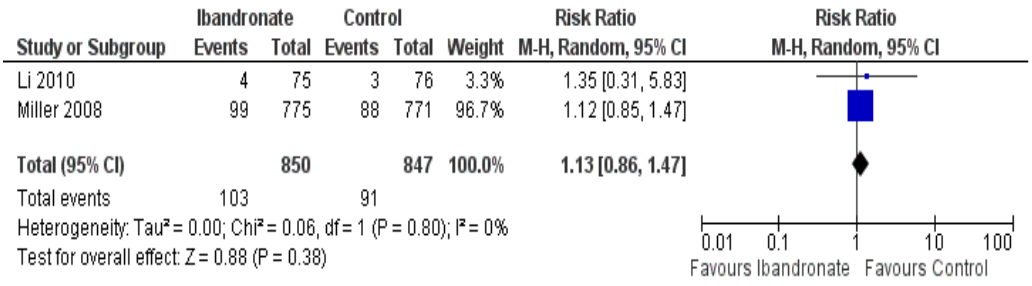
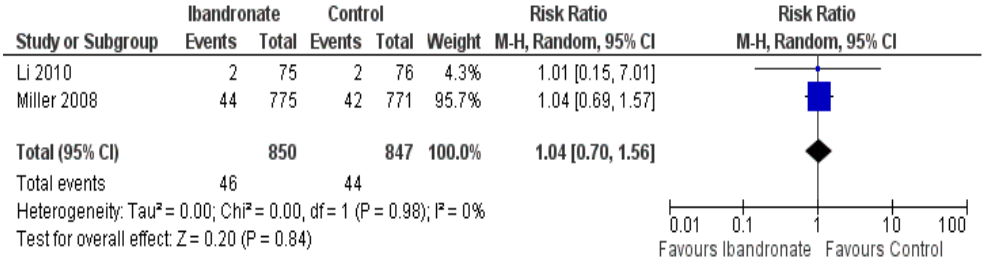


Figure 4e. Forest plot, ibandronate versus alendronate, follow-up denominators: Adverse event withdrawals.

.



APPENDIX 5 SEARCH STRATEGY FOR ZOLEDRONIC ACID RCTS

Databases: CENTRAL, DARE, HTA Database and NHS EED, The Cochrane Library, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to 2011>; EMBASE <1980 to 2011>; Scopus

1. exp Osteoporosis/ (39723)
2. osteoporo$.tw. (43172)
3. osteopeni$.tw. (6886)
4. Bone Density/ (34791)
5. (bone$ adj fragil$).tw. (971)
6. exp Fractures, Bone/ (126227)
7. bone loss.tw. (16222)
8. bmd.tw. (16319)
9. bone mineral densit$.tw. (22449)
10. or/1-9 (196642)
11. zolendronate.tw. (24)
12. (Zoledronic adj2 acid).tw. (1502)
13. zolendron$.tw. (42)
14. zometa.tw. (92)
15. reclast.tw. (8)
16. zomera.tw. (1)
17. aclasta.tw. (7)
18. DB00399.tw. (0)
19. or/11-18 (1564)
20. randomized controlled trial.pt. (319995)
21. controlled clinical trial.pt. (83531)
22. randomized.ab. (235629)
23. placebo.ab. (132966)
24. drug therapy.fs. (1501280)
25. randomly.ab. (173342)
26. trial.ab. (243319)
27. groups.ab. (1136791)
28. or/20-27 (2868478)
29. exp animals/ not humans.sh. (3663238)
30. 28 not 29 (2447729)
31. 10 and 19 and 30 (410)

APPENDIX 6 LIST OF EXCLUDED ZOLEDRONIC ACID STUDIES (after full text retrieval)[123-135]

Study ID/First Author	Year	Reason for exclusion
Bachmann	2011	Lack of fracture outcome
Boonen	2010	Duplicate of another study or earlier report
Boonen	2011	Duplicate of another study or earlier report
Devogelaer	2007	Did not meet inclusion criteria
Grey	2009a	Follow-up from previous study/earlier report
Grey	2009b	Duplicate of another study or earlier report
Grey	2010	Follow-up from previous study/earlier report
Hwang	2011	Duplicate of another study or earlier report
Lyles	2007	Lack of useable fracture data
McClung	2007	Lack of fracture outcome
McClung	2009	Lack of useable fracture data
Reid	2002	Did not meet inclusion criteria
Saag	2007	Duration of therapy less than 1 year

APPENDIX 7 CHARACTERISTICS OF INCLUDED ZOLEDRONIC ACID STUDIES

Author and Year	Study Design	Doses used	Number in treatment and control groups	Patient Characteristics	Outcomes
Black 2007[136]	Randomized controlled trial Secondary prevention Duration 3 years Blinding: Double-blind, placebo-controlled, blinded radiologists	Zoledronic acid 5 mg iv at baseline, 12 months and 24 months Placebo iv at baseline, 12 months and 24 months All participants received daily Ca (1000-1500 mg) and vitamin D (400-1200 IU)	Zoledronic acid 5 mg N = 3889 Placebo N= 3876	Inclusion Criteria: Postmenopausal women between 65 and 89 years, BMD T score -2.5 or less at femoral neck with or without vertebral fracture, or -1.5 or less with at least 2 mild vertebral fractures or one moderate vertebral fracture) Exclusion Criteria: previous use parathyroid hormone, sodium fluoride, anabolic steroids or growth hormone within past 6 months, corticosteroids within past 12 months, hypercalcemic or poor renal function Zoledronic acid - mean age 73.1 years (SD 5.34), patients with 1 vertebral fracture 1093 (28.2%) Placebo - mean age 73.0 years (SD 5.40), patients with 1 vertebral fracture 1076 (27.9%)	Primary endpoints: Vertebral and hip fracture. Secondary endpoints: non-vertebral, clinical fracture, clinical vertebral fracture, changes in BMD, markers of bone resorption [(serum C-terminal telopeptide of type 1 collagen (sCTX)] and formation. Spinal lateral radiographs were done at baseline, 12, 24, and 36 months. Clinical fracture reports were confirmed centrally by radiologic/surgical report or copy of radiograph.
Grey 2012[137]	Randomized controlled trial Primary prevention	Zoledronic acid 1 mg iv at baseline Zoledronic acid 2.5 mg iv at baseline	Zoledronic acid 1 mg iv N = 45 Zoledronic acid 2.5 mg iv N = 45 Zoledronic acid 5 mg iv N = 45	Inclusion Criteria: postmenopausal women (more than 5 years) with a lumbar spine or a total hip BMD T score between -1 and -2. Exclusion Criteria: current use of	Fractures were a safety outcome along with other adverse events. Primary endpoint:

	Duration 1 year Blinding: Double-blind, placebo-controlled, blinded radiologists	Zoledronic acid 5 mg iv at baseline Placebo iv at baseline	Placebo iv N = 45	anti-resorptive therapies, hip or spine BMD $\leq$ -2.5, previous hip fracture, previous clinical vertebral fracture, previous postmenopausal wrist fracture, any past use of aminobisphosphonate or etidronate in past 3 years, Serum 25(OH)D less than 30 nmol/L, major systemic illness. Zoledronic acid - mean age 66 year (SD 8) Placebo - mean age 65 years (SD 9) Vertebral Fractures: none	relative change (%) from baseline in mean lumbar spine (L1-L4) BMD at 12 months of treatment. Secondary efficacy endpoints included: relative (%) change in mean BMD from baseline at total hip and total body and change in bone resorption marker serum C-terminal telopeptide of type 1 collagen (βCTX) from baseline, and change in procollagen type-I N-terminal propeptide (P1NP).

APPENDIX 8 MTC MODELS IN WINBUGS

MTC Code

WinBUGS (Bayesian inference Using Gibbs Sampling) is a software program that can be used for the Bayesian analysis of statistical models using Markov Chain Monte Carlo (MCMC) methods. Bayesian inference can be used to fit complex models that include both direct and indirect treatment comparisons. The WinBUGS model used for this thesis was based on the examples found at https://www.bris.ac.uk/cobm/research/mpes/mtc.html.

Prior to performing an analysis using a WinBUGS model, data must be formatted in a specific manner so that the program can read the data. First, the number of observations must be outlined by entering the following constants within a bracket after "LIST": where N = Number of arms, NS = Number of studies, and NT = Number of treatments.

The first line in the data set provides the variable names followed by brackets. Each following line is considered as a data line by WinBUGS. "END" is placed at the end of the list and indicates the end of data entry. At least one blank line has to be included after the “END” statement to allow the program to run.

The treatments A, B, C,…must be assigned treatment numbers such as 1,2,3, … etc. in the WinBUGS data. Placebo treatment is assigned as treatment A and is therefore coded with 1. The trials are then listed in a systematic order which is maintained in the WinBUGS data listing.

The following example shows the data entry for the outcome ‘hip fractures’ for 11 trials and 5 treatments [placebo, alendronate, etidronate, risedronate, zolendronic acid], where r[,1] indicates the numerator for treatment arm 1, n[,1] the denominator for treatment arm 1,t[] the treatment, and na [] the number of treatment arms.

r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	t[,2]	na[]
11	1022	22	1005	2	1	2
0	60	1	60	2	1	2
2	950	3	958	2	1	2
2	164	4	163	2	1	2
1	90	0	90	2	1	2
1	50	2	50	3	1	2
1	105	0	104	3	1	2
1	33	1	33	3	1	2
12	821	15	820	4	1	2
137	6197	95	3134	4	1	2
52	3889	88	3876	5	1	2

END

The model can be implemented using the tool bar buttons for each analysis or by using a "script" which provides the software with a list of instructions about which data to use, which model to use, and which steps to follow. An example of a script that was used for this study is:

```
# open log file
display('log')

# Check the syntax of the model file
check('C:/Users/Owner/Desktop/AllHipFract/ModelMTCBinRE.txt')

# Load data from data file #1
data('C:/Users/Owner/Desktop/AllHipFract/DataAllHipFractB.txt')

# Load data from data file #2
data('C:/Users/Owner/Desktop/AllHipFract/DataAllHipFractBD.txt')

# Compile two chains
compile(3)

# provide initial values for the first chain
inits(1,'C:/Users/Owner/Desktop/AllHipFract/Inits1FEAllHipFract.txt')

# provide initial values for the second chain
inits(2,'C:/Users/Owner/Desktop/AllHipFract/Inits2FEAllHipFract.txt')

# provide initial values for the first chain
inits(3,'C:/Users/Owner/Desktop/AllHipFract/Inits3FEAllHipFract.txt')
```

```
#generate random initial values for uninitialized chains
gen.inits()

# generate 40000 iterations as burnin
update(40000)

# Monitor the following parameters/nodes
set(delta)
set(T)
set(p)
set(dev)
set(resdev)
set(r.hat)
set(d)
set(or)
set(lor)
set(sdev)
set(rk)

# Monitor dic values
dic.set()

#Refresh plot and chain for every 100 iterations
refresh(100)

# Update each chain by 40,000 iterations (80,000 total)
update(40000)

# Calculate the (posterior) statistics for monitored parameters
stats(*)

#Calculate the DIC value
dic.stats()

# see Trace plots for monitored parameters
history(*)

# Plot Gelman-Ruban convergence diagnostic
gr(or)
```

A variety of additional functions are available and a detailed description can be found in the WinBUGS manual, which can be downloaded via this weblink: http://www.mrcbsu.cam.ac.uk/bugs/winbugs/manual14.pdf

As previously mentioned, a random effects model was used as the primary analysis for this thesis. The following model was used:

```
model{
for(i in 1:NS){
        w[i,1] <-0
              delta[i,1]<-0
              mu[i] ~ dnorm(0,.0001)              # vague priors for baselines
              for (k in 1:na[i])  {
                    r[i,k] ~ dbin(p[i,k],n[i,k])       # binomial likelihood
           logit(p[i,k])<-mu[i] + delta[i,k]                  # model
           r0[i,k]<-r[i,k]+0.01*equals(r[i,k],0) -0.01*equals(r[i,k],n[i,k])
                    p0[i,k]<- max(p[i,k],.001)
                    r.hat[i,k]<- p0[i,k]*n[i,k]
                                                    #Deviance calculation for binomial data
                    dev[i,k]<- 2*(r0[i,k]*log(r0[i,k]/r.hat[i,k]) + (n[i,k] - r0[i,k])*log((n[i,k] -
r0[i,k])/(n[i,k] - r.hat[i,k])))
                    }
                     for (k in 2:na[i]) {
  delta[i,k] ~ dnorm(md[i,k],taud[i,k])           # trial-specific LOR distributions
  md[i,k] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]              # mean of LOR distributions
  taud[i,k] <- tau *2*(k-1)/k                        #precision of LOR distributions
  w[i,k] <- (delta[i,k]  - d[t[i,k]] + d[t[i,1]])        #adjustment, multi-arm RCTs
  sw[i,k] <-sum(w[i,1:k-1])/(k-1)               # cumulative adjustment for multi-arm trials
                    }
               sdev[i]<-sum(dev[i,1:na[i]])
  }
resdev<-sum(sdev[])
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }         #  vague priors for basic parameters
tausq~dlnorm(-4.06,0.48)                    #  Informative prior for random effects variance
tau<-1/tausq
sd<-sqrt(tausq)
                              # Treatment 1 baseline, based on average of NP trials including it.
for (i in 1:NS) { mu1[i] <- mu[i] * equals(t[i,1],1) }
for (k in 1:NT)  { logit(T[k])<- (sum(mu1[])/NP) +d[k] }
                                                                        # ranking
for (k in 1:NT) { rk[k]<- rank(T[],k)
                    best[k]<-equals(rk[k],1)}
                                                                    # pairwise ORs
for (c in 1:(NT-1)) {  for (k in (c+1):NT)  { or[c,k] <- exp(d[k] - d[c] )
lor[c,k]<-d[k]-d[c]
}  }

}
```

Further information on available models by Ades et al can be found at: www.bris.ac.uk/cobm/docs/intro%20to%20mtc.doc

Several posterior distributions for various variables of interest are found in the output of these models, including: *d,* the mean treatment effect (i.e. dAB = mean treatment effect log odds ratio A versus B); *T,* the absolute efficacy T[k] of each treatment k; *p,* the probability of response in the respective treatment arms; *best,* the probability that each treatment is the best; and *lor* and *or* are all the possible log odds ratios and odds ratios for each comparison between treatments.

Throughout this thesis, odds ratios and 95% credible intervals are reported.

For the analyses in this thesis, some modifications of the model were performed to use predictive distributions based on a study of heterogeneity in meta-analyses (Turner 2012). The predictive distributions used were those obtained from objective outcomes such as all-cause mortality. Given the outcomes examined in this thesis, fracture outcome and withdrawals from studies, these were considered "objective" outcomes and those prior distributions were used. The informative priors in the original code were replaced with the following code:

```
tausq~dlnorm(-4.06,0.48)
tau<-1/tausq
sd<-sqrt(tausq)
```

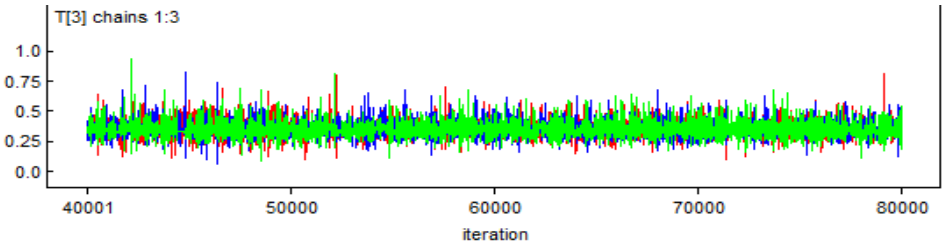
Convergence assessment

Convergence is reached when inferences do not depend on the initial starting values of the chains, and was assessed by two methods: history plots and Brooks-Gelman-Rubin plots. For history plots, two chains were simulated starting from different initial values of select unknown parameters and observed against the iteration number. Histories that overlap and appear to mix with each other, were considered to have achieved convergent. Brooks-Gelman-Rubin plots were then generated to control convergence. The Gelman-

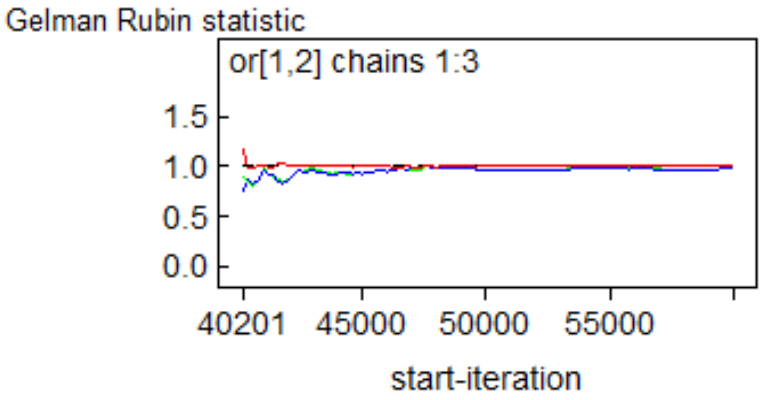
Rubin convergence statistic R compares the ratio of the pooled chain variance to the within variance. These are two ways to estimate the posterior variance. Once convergence is reached, R=1. Gelman-Rubin statistic (grey dashed lined) is which should converge to 1. Examples of these plots are shown in Figure 1**.**

Figure 1. Plots of convergence assessment.

A) History plot



B) Brooks Gelman Rubin plot



The Monte Carlo (MC) error for each parameter of interest was also reviewed to verify the accuracy of the posterior estimates. The MC error can be generated as part of the statistical output by including the command in the script or by the *stats* button in the sample monitor tool. The MC error estimates to what extent simulation error contributes

to uncertainty in the estimation of the mean. Ideally the MC error should be less than about 5% of the sample standard deviation.

No modifications were made to the seed, which specifies the random seed number used to initialize the random number generation procedure.

Fixed effects models

As a sensitivity analysis, fixed effects models were run to compare against the random effects models. In comparison to fixed effects models, the point estimates of the odds ratios from the random effects model were similar but for some outcomes the credible intervals were extremely large and varied greatly. This has been previously described (Lambert PC et al. *Stat Med.* 2005; 24(15):2401), and is frequently observed when a small number of trials are available, and this was seen in the present analysis.

```
model{
for(i in 1:NS){
            delta[i,1]<-0
            mu[i] ~ dnorm(0,.0001)                    # vague priors for baselines
            for (k in 1:na[i])  {
                  r[i,k] ~ dbin(p[i,k],n[i,k])              # binomial likelihood
         logit(p[i,k])<-mu[i] + delta[i,k]                        # model
         r0[i,k]<-r[i,k]+0.01*equals(r[i,k],0) -0.01*equals(r[i,k],n[i,k])
                  p0[i,k]<- max(p[i,k],.001)
                  r.hat[i,k]<- p0[i,k]*n[i,k]
                              #Deviance calculation for binomial data
                  dev[i,k]<- 2*(r0[i,k]*log(r0[i,k]/r.hat[i,k]) + (n[i,k] - r0[i,k])*log((n[i,k] -
r0[i,k])/(n[i,k] - r.hat[i,k])))
                  }
                   for (k in 2:na[i]) {
            delta[i,k] <- d[t[i,k]] - d[t[i,1]]
                  }
             sdev[i]<-sum(dev[i,1:na[i]])
  }
resdev<-sum(sdev[])
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }                #  vague priors for basic parameters
                        # Treatment 1 baseline, based on average of NP trials including it.
for (i in 1:NS) { mu1[i] <- mu[i] * equals(t[i,1],1) }
for (k in 1:NT)  { logit(T[k])<- (sum(mu1[])/NP) +d[k] }
                                                                  # ranking
```

```
for (k in 1:NT) { rk[k]<- rank(T[],k)
                  best[k]<-equals(rk[k],1)}                    # pairwise ORs
for (c in 1:(NT-1)) {  for (k in (c+1):NT)  { or[c,k] <- exp(d[k] - d[c] )
}  }
```

APPENDIX 9 ASSESSMENT OF CONSISTENCY

In reporting on the results of network meta-analysis, it is recommended that models be evaluated for inconsistency. Inconsistency has been described as the conflict between "direct" evidence on a comparison between treatments B and C, and "indirect" evidence gained from the examination of AC and AB trials, where treatments B and C have been compared to a common intervention, A. Inconsistency is caused by effect modifiers, and specifically by an imbalance in the distribution of effect modifiers in the direct and indirect evidence (Dias et al 2011). Checking for inconsistency is therefore recommended in addition to considerations of the extent of heterogeneity and its sources. Heterogeneity can be characterized as between-trial variation within treatment contrasts, and inconsistency as variation between treatment contrasts.

There are several methods available to test for inconsistency, including comparing the standard network consistency model to an "inconsistency", or unrelated mean effects, model. A WinBUGS code has been developed to implement random and effects inconsistency models in a Bayesian framework and the codes can be found at:
The inconsistency random effects model below was used to create the posterior mean deviance contributions and these were plotted against those obtained from the consistency models to assess for inconsistency (Technical Document Dias 2011).

The model used was as follows:

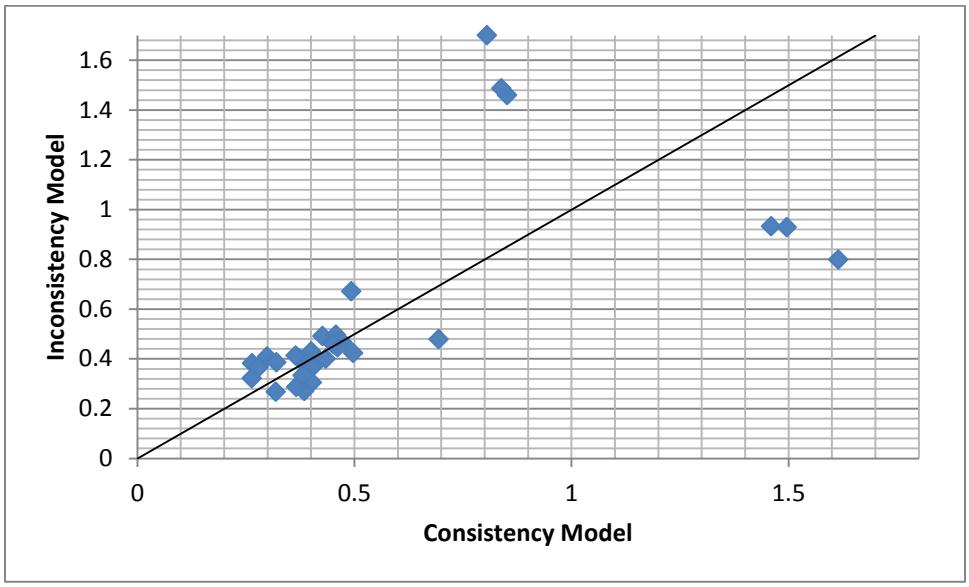
```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:NS){             # LOOP THROUGH STUDIES
   delta[i,1]<-0          # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

```
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(NT-1)) {  # priors for all mean treatment effects
   for (k in (c+1):NT)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS
```

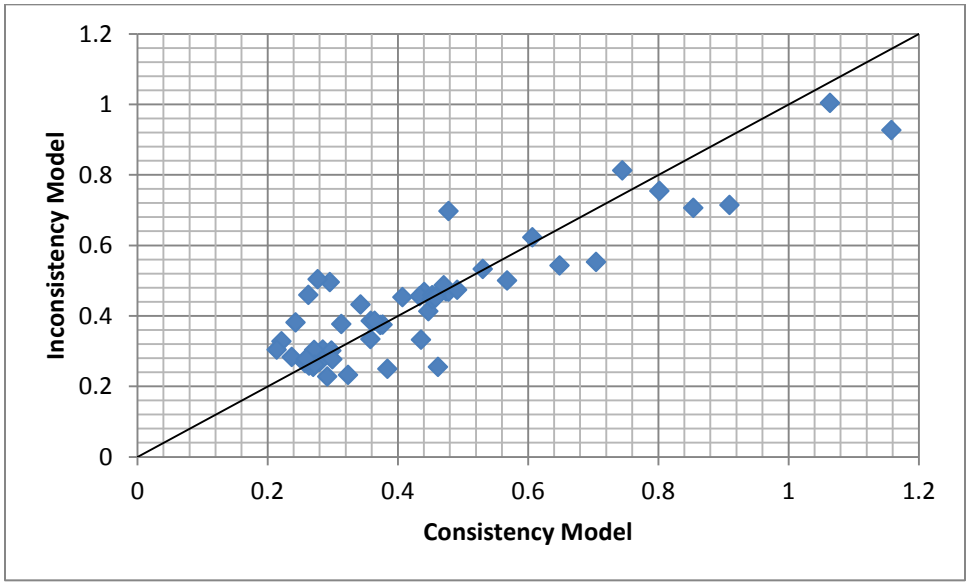
The figures below show the results of plotting the posterior mean deviance contributions for the consistency and inconsistency models for each of the following outcomes: vertebral, non-vertebral, hip and wrist fractures, and total and adverse event withdrawals. Plotting the posterior mean deviance of the individual data points in the inconsistency models against their posterior mean deviance in the consistency model can help identify when inconsistency is present. Points that show a much lower value of the posterior mean deviance in the inconsistency model (below the line of equality), suggest that a consistency model does not fit these points well. In general, trial-arms with zero cells will have a high posterior mean of the residual deviance as the models will never predict a zero cell exactly. Overall this is what was observed in the plots presented below. For vertebral fractures, the outliers from the line of equality were smaller trials where zero events were observed in a treatment arm, but the majority of points are close to the line of equality, suggesting that there is minimal inconsistency. Somewhat more inconsistency was seen in the other fracture outcomes, which is not unexpected given that not all the trials included were designed to detect these outcomes. In particular for hip and wrist fractures there were fewer studies and fewer events, which yielded higher residual deviance values.

Figure 1. Plots of the individual data points' posterior mean deviance contributions for the consistency model (horizontal axis) and the inconsistency model (vertical axis) along with the line of equality.

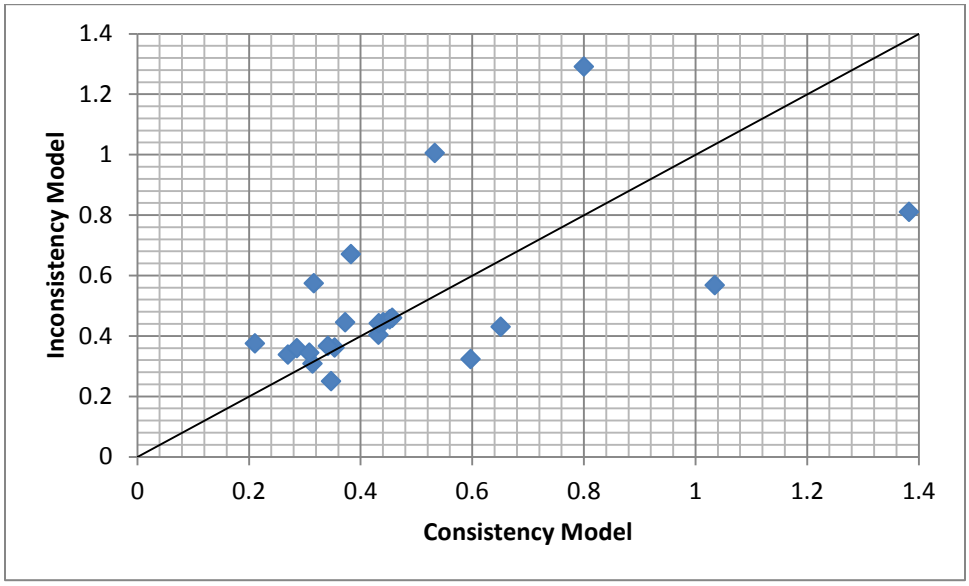
A) Vertebral fractures



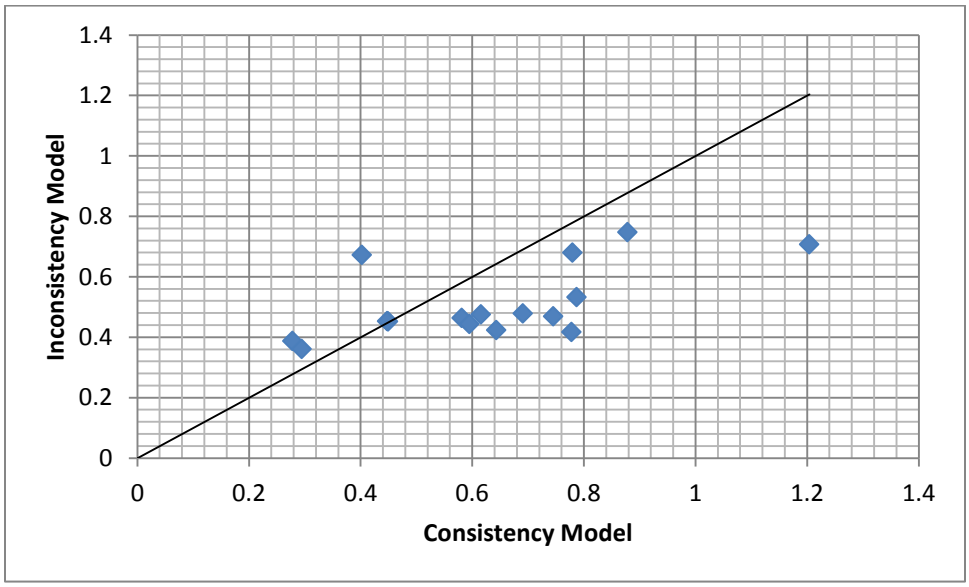
B) Non-vertebral fractures



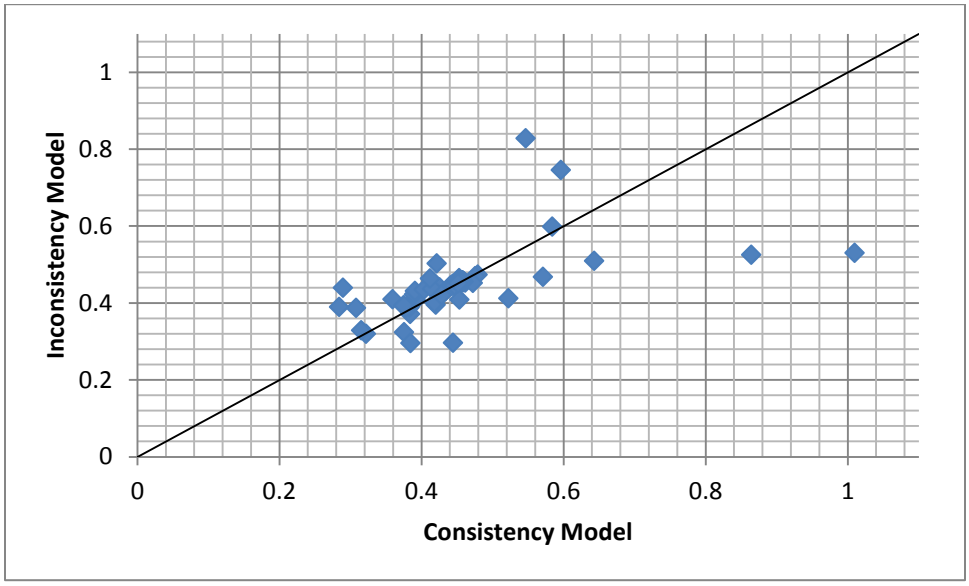
C) Hip fractures



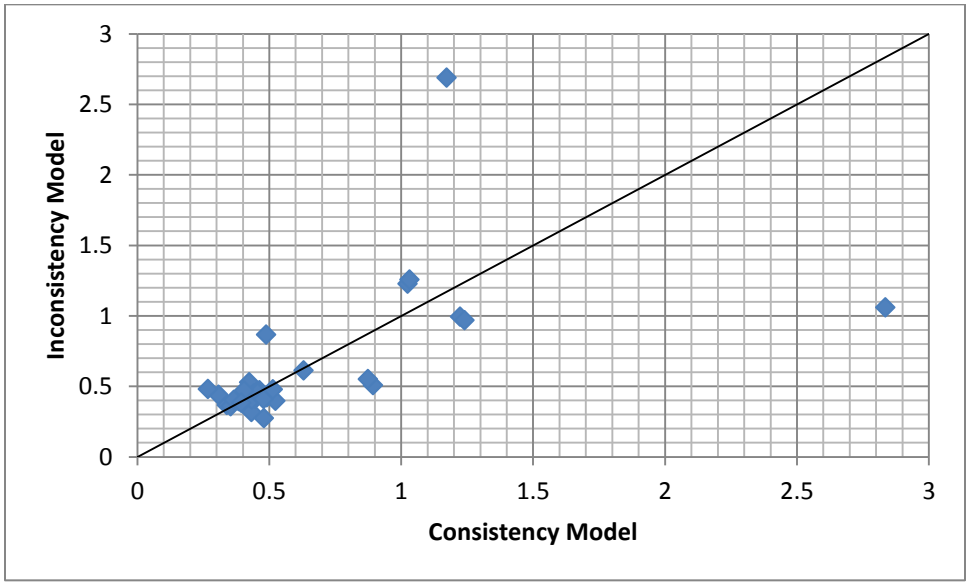
D) Wrist fractures



E) Total withdrawals



F) Adverse event withdrawals



APPENDIX 10 MTC MODELS IN SAS: PROC GLIMMIX

PROC GLIMMIX is a procedure in SAS for fitting **G**eneralized **L**inear **M**ixed **M**odels, where the data can have any distribution from the exponential family. Examples comprise the normal, beta and gamma distributions as continuous members and the binary, binomial and Poisson distributions as discrete members

Throughout this thesis the following model was used for the random effects analyses:

```
/*Random-effect model*/
ods output diffs=OR;
proc glimmix data=AllvertfractBD;
class STUDY DRUG;
format drug drug.;
model event/n = DRUG / solution oddsratio noint ddfm=satterth covb;
random STUDY;
lsmeans DRUG / ilink pdiff cl;
run;
ods output;

/*Use ods output to generate all pairwise comparisons*/
data OR(keep=DRUG _DRUG estimate lower upper);set OR;
estimate=exp(Estimate);lower=exp(lower);upper=exp(upper);
run;

proc print data=OR;run;
```

First, the ODS OUTPUT statement instructs the program how to consider the diffs output as OR. This is linked to the later DATA statement below which instructs the program how to tabulate the output data.

The PROC GLIMMIX statement begins the procedure and instructs the program to use the specific data file (in this example AllvertfractBD).

The CLASS statement instructs the procedure to treat the variables *Study* and *Drug* as classification variables. It must appear before the MODEL statement.

The FORMAT statement instructs the procedure to format the variable drug.

The MODEL statement names the dependent variable (event/n) and the fixed effects (*Drug*). This syntax is specific to models for binomial data and so the GLIMMIX procedure automatically defaults to the binomial distribution. Once the distribution is

determined, the procedure selects the link function for the model. The default link for binomial data is the logit link. The statement option for model building NOINT excludes the fixed effects intercept from the model. SOLUTION and ODDSRATIO are model statement options for the statistical output. SOLUTION displays fixed effects, while ODDSRATIO displays odds ratios and confidence limits. DDFM= is a statement option for statistical computations and specifies the method for computing the denominator's degrees of freedom. In this case, the DDFM=SATTERTH option performs a general Satterthwaite approximation for the denominator degrees of freedom in the model. The COVB option results in the generation of covariance values for each drug-drug comparison.

The RANDOM statement identifies the random effects, which was the variable *Study*.

The LSMEANS statement computes least squares (LS) means of fixed effects (*Drug*). ILINK and CL are statement options of the statistical output. ILINK computes and displays estimates and standard errors of LS means on the inverse linked scale. CL constructs confidence limits for means and mean differences. PDIFF requests differences of LS means.

The RUN statement tells SAS to process the preceding program statements.

The DATA statement after ODS OUTPUT tells the program to generate pairwise comparisons for all the drugs and display the odds ratios and confidence levels.

The PROC PRINT statement tells the program to print the output data as previously generated.

The following model was used for the fixed effects analyses:

```
/*Fixed-effect model*/
ods output diffs=OR;
proc glimmix data=AllvertfractBD;
class STUDY DRUG;
format drug drug.;
model event/n = DRUG / solution oddsratio noint ddfm=satterth covb;
```

```
lsmeans DRUG / ilink pdiff cl;
run;
ods output;

/*Use ods output to generate all pairwise comparisons*/
data OR(keep=DRUG _DRUG estimate lower upper);set OR;
estimate=exp(Estimate);lower=exp(lower);upper=exp(upper);
run;

proc print data=OR;run;
```

APPENDIX 11 INCLUDED STUDIES FOR MTC ANALYSES

Table 1a. Studies included for vertebral fractures analyses.

Study ID/First Author	Year	Reference
Black	1996	140
Black	2007	136
Bone	1997	141
Chesnut	2004	118
Cummings	1998	142
Dursun	2001	143
Fogelman	2000	144
Harris	1999	145
Hooper	2005	146
Lyritis	1997	147
Menuier	1997	148
Miller	2008	62
Montessori	1997	149
Pouilles	1997	150
Reginster	2000	151
Watts	1990	152
Wimalawansa	1998	153

Table 1b. Studies included for non-vertebral fractures analyses.

Study ID/First Author	Year	Reference
Black	1996	140
Black	2007	136
Bone	1997	141
Chesnut	2004	118
Cummings	1998	142
Fogelman	2000	144
Grey	2012	137
Harris	1999	145
Hooper	2005	146
Hosking	1998	154
Ishida	2004	155
Li	2010	121
Lyritis	1997	147
McClung	2001	156
McClung	2004	108
McClung	2009	120
Menieur	1997	148
Miller	2008	62
Pols	1999	157
Pouilles	1997	150
Qin	2001	158
Reginster	2000	151
Storm	1990	159
Valimake	2007	160
Watts	1990	152
Wimalawansa	1998	153
Yan	2009	161

Table 1c. Studies included for hip fractures analyses.

Study ID/First Author	Year	Reference
Black	1996	140
Black	2007	136
Fitzpatrick	2011	162
Greenspan	1998	163
Greenspan	2002	164
Harris	1999	145
Lyritis	1997	147
McClung	2001	156
Pols	1999	157
Storm	1990	159
Watts	1990	152

Table 1d. Studies included for wrist fractures analyses.

Study ID/First Author	Year	Reference
Black	1996	140
Cummings	1998	142
Harris	1999	145
Lyritis	1997	147
Pols	1999	157
Valimake	2007	160
Watts	1990	152
Yan	2009	161

Table 1e. Studies included for total withdrawals analyses.

Study ID/First Author	Year	Reference
Ascott Evans	2003	165
Black	1996	136
Black	2007	140
Chesnut	2004	118
Cummings	1998	142
Fogelman	2000	144
Greenspan	1998	163
Grey	2012	137
Harris	1999	145
Herd	1997	166
Hooper	2005	146
Hosking	1998	154
Kung	2000	167
Li	2005	168
Li	2010	121
Lyritis	1997	147
McClung	2001	156
McClung	2009	120
Menuier	1997	148
Miller	2008	62
Montessori	1997	149
Pols	1999	157
Pouilles	1997	150
Qin	2007	158
Reginster	2000	151
Storm	1990	159
Watts	1990	152
Wimalawansa	1998	153
Yan	2009	161

Table 1f. Studies included for adverse events withdrawals analyses.

Study ID/First Author	Year	Reference
Ascott Evans	2003	165
Black	1996	140
Black	2007	136
Bone	1997	141
Chesnut	2004	118
Cummings	1998	142
Fogelman	2000	144
Harris	1999	145
Herd	1997	166
Hooper	2005	146
Hosking	1998	154
Li	2005	168
McClung	2001	156
McClung	2009	120
Menuier	1997	148
Miller	2008	62
Montessori	1997	149
Pols	1999	157
Pouilles	1997	150
Reginster	2000	151
Storm	1990	159
Valimaki	2007	160
Watts	1990	152
Wimalawansa	1998	153
Yan	2009	161

Table 1g. Characteristics of studies added to the network meta-analyses.

Author and Year	Study Design	Drugs and Doses used	Number in treatment and control groups	Patient Characteristics	Outcomes
Fitzpatrick 2011[162]	Randomized controlled trial Secondary prevention Duration 1 year Blinding: Double-blind, placebo-controlled	Alendronate 70 mg po weekly Placebo po weekly All participants received daily Ca (500-660 mg elemental and vitamin D (at least 400 IU)	Alendronate 70 mg N = 90 Placebo N= 90	Inclusion Criteria: Postmenopausal women (at least 5 years), BMD T score ≤ -2.5 (with no vertebral fracture) or ≤ -2.0 (if 1 vertebral fracture) or at the femoral neck, total hip, trochanter, or lumbar spine Exclusion Criteria: more than 2 vertebral fracture or any non-vertebral osteoporosis-related fragility fracture after age of 40; vitamin D deficiency, metabolic bone disease, previous use osteoporosis treatments Alendronate - mean age 65.1 years (SD 7.04), patients with 1 vertebral fracture 36 (40%) Placebo - mean age 63.2 years (SD 6.75), patients with 1 vertebral fracture 41 (46%)	Primary endpoints: BMD, markers of bone resorption serum C-terminal telopeptide of type 1 collagen (CTX1), marker of bone formation procollagen type 1 N propeptide (P1NP) Secondary endpoints: adverse events including fractures
Kung 2000[167]	Randomized controlled trial Secondary	Alendronate 10 mg po daily Placebo po daily	Alendronate 10 mg po N = 35 Placebo N = 35	Inclusion Criteria: postmenopausal women (more than 3 years) < 75 years with a lumbar spine < 2.5 SD of local mean value. Exclusion Criteria: bisphosphonate	Primary endpoints: BMD, serum Ca, phosphorus, alkaline phosphatase Secondary endpoints:

	prevention Duration 1 year Blinding: Double-blind, placebo-controlled	All participants received daily Ca 500 mg		or fluoride therapy within past 12 months, use of HRT and calcitonin in previous 6 months, history metabolic bone disease, impaired renal or liver function, history of major gastrointestinal disease, other major medical illness. Alendronate 10 mg po - mean age 64 years (SD 5), 12 with vertebral fracture Placebo - mean age 65 years (SD 4), 14 with vertebral fracture	adverse events
Li 2005[168]	Randomized controlled trial Secondary prevention Duration 1 year Blinding: Double-blind, placebo-controlled	Risedronate 5 mg po daily Placebo po daily All participants received daily Ca 600 mg	Risedronate mg po N = 30 Placebo N = 30	Inclusion Criteria: postmenopausal women (more than 1 year) between 45 and 68 years, with a lumbar spine T-score ≥- 2.5 SD Exclusion Criteria: history metabolic bone disease, history of use of drugs affecting bone metabolism Mean age of participants not provided	Primary endpoints: BMD at lumbar spine (L2-L4) Secondary endpoints: BMD at hip, adverse events
Qin 2007[158]	Randomized controlled trial Secondary prevention Duration 1 year Blinding: Double-	Alendronate 10 mg po daily Placebo po daily All participants received daily Ca 1200 mg	Alendronate 10 mg po N = 22 Placebo po N = 25	Inclusion Criteria: Postmenopausal women between 50-75 years with a history of distal radial fracture and BMD T scores ≤ -2 at the spine or hip Exclusion Criteria: HRT or drug treatment known to affect bone metabolism; thyroid, parathyroid,	Primary endpoints: BMD at spine and femoral neck Secondary endpoints: serum alkaline phosphatase, urinary deoxypyridoline,

	blind, placebo-controlled			renal or liver disease; gastrointestinal tract disease. Alendronate - mean age 60.7 years (SD 6.4), patients with vertebral fracture not stated Placebo - mean age 59.1 years (SD 6.3), patients with vertebral fracture not stated	adverse events
Valimaki 2007[160]	Randomized controlled trial Secondary prevention Duration 1 year Blinding: Double-blind, placebo-controlled	Risedronate 5 mg po daily Placebo po daily All participants received daily Ca 1000 mg and vitamin D 400 IU	Risedronate 5 mg po N = 116 Placebo N = 56	Inclusion Criteria: Postmenopausal women (≥ 5 years) with a baseline lumbar spine BMD T scores between -2.5 and -1, plus ≥ 1 risk factor for osteoporosis such as premature menopause or hip osteopenia. Exclusion Criteria: cancer in past 5 years, osteoarthritis, long –term treatment with corticosteroids, spinal fusion, > 2 fractured lumbar vertebrae, recent bisphosphonate therapy (within 6 months). Risedronate - mean age 66.1 years (SD 6.8), patients with vertebral fracture not stated Placebo - mean age 65.4 years (SD 6.8), patients with vertebral fracture not stated	Primary endpoints: change in lumbar spine BMD Secondary endpoints: Bone turnover markers urinary type I collagen cross-linked N-telopeptide and serum bone-specific alkaline phosphatase, adverse events.
Yan 2009[161]	Randomized	Alendronate 70 mg po weekly	Alendronate 70 mg po N = 280	Inclusion Criteria: Postmenopausal women (≥ 3 years) less than 85 years, with a baseline lumbar spine	Primary endpoints: change in lumbar

	controlled trial Secondary prevention Duration 1 year Blinding: Double-blind, placebo-controlled	Placebo po weekly All participants received daily Ca (500 mg and vitamin D 200 IU)	Placebo N = 260	BMD T scores less than – 2, who did not have prevalent vertebral fractures Exclusion Criteria: diseases of bone metabolism; liver, renal, or heart disease; bisphosphonate, anabolic steroid or estrogen or estrogen-related drugs in the last 12 months. Alendronate - mean age 65.2 years (SD 6.5), patients with vertebral fracture 0 Placebo - mean age 64.7 years (SD 5.9), patients with vertebral fracture 0	spine BMD Secondary endpoints: Bone turnover markers urinary type I collagen cross-linked N-telopeptide and serum bone-specific alkaline phosphatase, adverse events.

Table 1 h. Excluded studies from previously conducted meta-analyses[169-174].

Study ID/First Author	Year	Drug	Reason for exclusion
Chesnut	1995	Alendronate	No useable data
Clemmesen	1997	Risedronate	Did not meet inclusion criteria
Liberman	1995	Alendronate	Unclear time for outcome
Mortensen	1998	Risedronate	Unclear time for outcome
Pacifici	1988	Etidronate	No useable data
Shiota	2001	Etidronate	Did not meet inclusion critera

APPENDIX 12 BAYESIAN MTC SENSITIVITY ANALYSES RESULTS

Table 1. Baseline versus follow-up denominators comparisons for bisphosphonates versus placebo.

A) Vertebral fractures.

Treatment	Baseline OR[a] (95% CrI[b])	Follow-up OR (95% CrI)
Alendronate 5 mg/day po	0.62 (0.15, 2.37)	0.60 (0.14, 2.34)
Alendronate 10 mg/day po	**0.53 (0.40, 0.71)**	**0.52 (0.39, 0.70)**
Etidronate 400 mg/month po	**0.47 (0.23, 0.94)**	**0.44 (0.21, 0.87)**
Ibandronate 150 mg/month po	0.51 (0.13, 1.96)	0.52 (0.13, 2.14)
Ibandronate 2.5 mg/day po	**0.49 (0.30, 0.79)**	**0.48 (0.29, 0.79)**
Ibandronate 20 mg intermittently po	**0.51 (0.32, 0.83)**	**0.53 (0.32, 0.85)**
Risedronate 150 mg/month po	**0.59 (0.48, 0.78)**	**0.59 (0.45, 0.78)**
Zoledronic acid 5 mg/year iv	**0.28 (0.20, 0.40)**	**0.28 (0.19, 0.39)**

[a]OR, Odds Ratio. [b]CrI, Credible Interval. Significant results are in bold font.

B) Non-vertebral fractures.

Treatment	Baseline OR[a] (95% CrI[b])	Follow-up OR (95% CrI)
Alendronate 5 mg/day po	1.02 (0.58, 1.78)	1.04 (0.59, 1.81)
Alendronate 10 mg/day po	**0.78 (0.59, 0.95)**	**0.78 (0.60, 0.96)**
Etidronate 400 mg/month po	0.67 (0.40, 1.10)	0.64 (0.37, 1.07)
Ibandronate 2 mg/every 3 months iv	0.82 (0.013, 46.85)	0.82 (0.030, 22.92)
Ibandronate 150 mg/month po	0.91 (0.41, 2.08)	0.92 (0.41, 2.04)
Ibandronate 2.5 mg/day po	1.11 (0.72, 1.69)	1.08 (0.71, 1.66)
Ibandronate 20 mg intermittently po	1.08 (0.70, 1.65)	1.02 (0.66, 1.58)
Risedronate 150 mg/month po	**0.75 (0.57, 0.91)**	**0.73 (0.57, 0.90)**
Zoledronic acid 5 mg/year iv	0.78 (0.53, 1.02)	0.74 (0.53, 1.03)

[a]OR, Odds Ratio. [b]CrI, Credible Interval. Significant results are in bold font.

C) Hip fractures.

Treatment	Baseline OR[a] (95% CrI[b])	Follow-up OR (95% CrI)
Alendronate 10 mg/day po	0.52 (0.26, 1.01)	0.53 (0.26, 1.07)
Etidronate 400 mg/month po	0.98 (0.15, 1.08)	0.98 (0.18, 5.32)
Risedronate 150 mg/month po	0.74 (0.51, 1.08)	0.73 (0.50, 1.08)
Zoledronic acid 5 mg/year iv	**0.58 (0.36, 0.94)**	**0.59 (0.36, 0.96)**

[a]OR, Odds Ratio. [b]CrI, Credible Interval. Significant results are in bold font.

D) Wrist fractures.

Treatment	Baseline OR[a] (95% CrI[b])	Follow-up OR (95% CrI)
Alendronate 10 mg/day po	0.73 (0.39, 1.12)	0.74 (0.39, 1.14)
Etidronate 400 mg/month po	2.29 (0.36, 19.9)	2.20 (0.37, 18.81)
Risedronate 150 mg/month po	0.61 (0.24, 1.49)	0.61 (0.24, 1.48)

[a]OR, Odds Ratio. [b]CrI, Credible Interval.

E) Total withdrawals.

Treatment	Baseline OR[a] (95% CrI[b])	Follow-up OR (95% CrI)
Alendronate 5 mg/day po	1.13 (0.32, 4.06)	1.18 (0.79, 1.76)
Alendronate 10 mg/day po	0.75 (0.46, 1.24)	1.12 (0.99, 1.38)
Etidronate 400 mg/month po	0.92 (0.50, 1.67)	0.91 (0.61, 1.37)
Ibandronate 2 mg/every 3 months iv	1.05 (0.13, 9.09)	1.62 (0.30, 8.57)
Ibandronate 150 mg/month po	1.18 (0.41, 3.67)	1.35 (0.93, 2.04)
Ibandronate 2.5 mg/day po	0.92 (0.27, 3.22)	0.84 (0.60, 1.16)
Ibandronate 20 mg intermittently po	0.86 (0.25, 2.99)	0.73 (0.53, 1.02)
Risedronate 150 mg/month po	0.82 (0.47, 1.42)	0.86 (0.72, 1.00)
Zoledronic acid 5 mg/year iv	0.96 (0.31, 3.02)	0.97 (0.74, 1.26)

[a]OR, Odds Ratio. [b]CrI, Credible Interval.

F) Adverse event withdrawals.

Treatment	Baseline OR[a] (95% CrI[b])	Follow-up OR (95% CrI)
Alendronate 5 mg/day po	1.02 (0.34, 3.03)	0.60 (0.26, 1.26)
Alendronate 10 mg/day po	0.97 (0.48, 1.96)	1.00 (0.63,1.57)
Etidronate 400 mg/month po	1.02 (0.40, 2.63)	1.04 (0.44, 2.45)
Ibandronate 150 mg/month po	1.41 (0.42, 5.07)	1.35 (0.56, 3.58)
Ibandronate 2.5 mg/day po	0.92 (0.23, 3.60)	9.92 (0.35, 2.41)
Ibandronate 20 mg intermittently po	0.86 (0.22, 3.42)	0.92 (0.35, 2.40)
Risedronate 150 mg/month po	0.93 (0.51, 1.70)	0.92 (0.59, 1.42)
Zoledronic acid 5 mg/year iv	1.16 (0.29, 4.62)	1.17 (0.45, 3.07)

[a]OR, Odds Ratio. [b]CrI, Credible Interval.

Table 2. Random versus fixed effects comparisons for bisphosphonates versus placebo.

A) Vertebral fractures.

Treatment	Random OR[a] (95% CrI[b])	Fixed OR (95% CrI)
Alendronate 5 mg/day po	0.62 (0.15, 2.37)	0.62 (0.15, 2.34)
Alendronate 10 mg/day po	**0.53 (0.40, 0.71)**	**0.52 (0.42, 0.65)**
Etidronate 400 mg/month po	**0.47 (0.23, 0.94)**	**0.47 (0.23, 0.92)**
Ibandronate 150 mg/month po	0.51 (0.13, 1.96)	0.51 (0.13, 1.93)
Ibandronate 2.5 mg/day po	**0.49 (0.30, 0.79)**	**0.49 (0.32, 0.72)**
Ibandronate 20 mg intermittently po	**0.51 (0.32, 0.83)**	**0.51 (0.34, 0.76)**
Risedronate 150 mg/month po	**0.59 (0.48, 0.78)**	**0.59 (0.47, 0.75)**
Zoledronic acid 5 mg/year iv	**0.28 (0.20, 0.40)**	**0.28 (0.22, 0.35)**

[a]OR, Odds Ratio. [b]CrI, Credible Interval. Significant results are in bold font.

B) Non-vertebral fractures.

Treatment	Random OR[a] (95% CrI[b])	Fixed OR (95% CrI)
Alendronate 5 mg/day po	1.02 (0.58, 1.78)	1.03 (0.61, 1.74)
Alendronate 10 mg/day po	**0.78 (0.59, 0.95)**	**0.81 (0.70, 0.93)**
Etidronate 400 mg/month po	0.67 (0.40, 1.10)	0.67 (0.40, 1.10)
Ibandronate 2 mg/every 3 months iv	0.82 (0.013, 46.85)	0.81 (0.20, 32.34)
Ibandronate 150 mg/month po	0.91 (0.41, 2.08)	0.95 (0.45, 2.01)
Ibandronate 2.5 mg/day po	1.11 (0.72, 1.69)	1.11 (0.81, 1.53)
Ibandronate 20 mg intermittently po	1.08 (0.70, 1.65)	1.08 (0.79, 1.49)
Risedronate 150 mg/month po	**0.75 (0.57, 0.91)**	**0.78 (0.69, 0.89)**
Zoledronic acid 5 mg/year iv	0.78 (0.53, 1.02)	0.73 (0.62, 0.86)

[a]OR, Odds Ratio. [b]CrI, Credible Interval. Significant results are in bold font.

C) Hip fractures.

Treatment	Random OR[a] (95% CrI[b])	Fixed OR (95% CrI)
Alendronate 10 mg/day po	0.52 (0.26, 1.01)	0.53 (0.26, 1.07)
Etidronate 400 mg/month po	0.98 (0.15, 1.08)	0.98 (0.18, 5.32)
Risedronate 150 mg/month po	0.74 (0.51, 1.08)	0.73 (0.50, 1.08)
Zoledronic acid 5 mg/year iv	**0.58 (0.36, 0.94)**	**0.59 (0.36, 0.96)**

[a]OR, Odds Ratio. [b]CrI, Credible Interval. Significant results are in bold font.

D) Wrist fractures.

Treatment	Random OR[a] (95% CrI[b])	Fixed OR (95% CrI)
Alendronate 10 mg/day po	0.73 (0.39, 1.12)	0.74 (0.39, 1.14)
Etidronate 400 mg/month po	2.29 (0.36, 19.9)	2.20 (0.37, 18.81)
Risedronate 150 mg/month po	0.61 (0.24, 1.49)	0.61 (0.24, 1.48)

[a]OR, Odds Ratio. [b]CrI, Credible Interval.

E) Total withdrawals.

Treatment	Random OR[a] (95% CrI[b])	Fixed OR (95% CrI)
Alendronate 5 mg/day po	1.13 (0.32, 4.06)	1.18 (0.79, 1.76)
Alendronate 10 mg/day po	0.75 (0.46, 1.24)	1.12 (0.99, 1.38)
Etidronate 400 mg/month po	0.92 (0.50, 1.67)	0.91 (0.61, 1.37)
Ibandronate 2 mg/every 3 months iv	1.05 (0.13, 9.09)	1.62 (0.30, 8.57)
Ibandronate 150 mg/month po	1.18 (0.41, 3.67)	1.35 (0.93, 2.04)
Ibandronate 2.5 mg/day po	0.92 (0.27, 3.22)	0.84 (0.60, 1.16)
Ibandronate 20 mg intermittently po	0.86 (0.25, 2.99)	0.73 (0.53, 1.02)
Risedronate 150 mg/month po	0.82 (0.47, 1.42)	0.86 (0.72, 1.00)
Zoledronic acid 5 mg/year iv	0.96 (0.31, 3.02)	0.97 (0.74, 1.26)

[a]OR, Odds Ratio. [b]CrI, Credible Interval.

F) Adverse event withdrawals.

Treatment	Random OR[a] (95% CrI[b])	Fixed OR (95% CrI)
Alendronate 5 mg/day po	1.02 (0.34, 3.03)	1.25 (0.82, 1.93)
Alendronate 10 mg/day po	0.97 (0.48, 1.96)	0.94 (0.81, 1.09)
Etidronate 400 mg/month po	1.02 (0.40, 2.63)	1.06 (0.52, 2.19)
Ibandronate 150 mg/month po	1.41 (0.42, 5.07)	1.07 (0.70, 1.67)
Ibandronate 2.5 mg/day po	0.92 (0.23, 3.60)	0.92 (0.76, 1.11)
Ibandronate 20 mg intermittently po	0.86 (0.22, 3.42)	0.86 (0.72, 1.04)
Risedronate 150 mg/month po	0.93 (0.51, 1.70)	0.97 (0.88, 1.07)
Zoledronic acid 5 mg/year iv	1.16 (0.29, 4.62)	1.16 (0.95, 1.42)

[a]OR, Odds Ratio. [b]CrI, Credible Interval.