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Bisphosphonates for the primary and secondary prevention of osteoporotic fractures in postmenopausal women: a meta-analysis

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Canadian Agency for Drugs and Technologies in Health

Bisphosphonates for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women: A Meta-Analysis

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October 2006

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Authorship

George Wells was involved in the conception, design, and implementation of the project, and contributed significantly to the writing of the first draft of the report. He was also significantly involved in revising subsequent draft versions, after the internal and external review of the report.

Ann Cranney was involved with the conception of the review, data abstraction, analysis, interpretation, and revision of the final report.

Michel Boucher assisted in the design of the analysis, reporting and interpretation of the findings, and was involved in the writing of the first draft of the report. He was also responsible for revisions to the subsequent drafts, after the internal and external review of the report, and responded to questions from copy editors and report formatters for the final version.

Joan Peterson screened the literature, was involved in the data abstraction, quality assessment and analysis of the primary trials, and assisted in revising all drafts of the report.

Beverley Shea was involved in developing the protocol, conducting the systematic review, and assisting in revising the final report.

Vivian Robinson was involved in developing the protocol, conducting the systematic review, and assisting in revising the final report.

Douglas Coyle assisted with the design of the review, and reviewed the analysis.

Peter Tugwell provided clinical rheumatology expertise, methodological guidance, and comments on all drafts.

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Conflicts of Interest

No conflicts of interest were declared by any author.

REPORT *IN BRIEF*

October 2006

Bisphosphonates for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women: A Meta-Analysis

Technology

Bisphosphonate drugs to prevent osteoporotic fractures: etidronate, alendronate, and risedronate.

Condition

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture. In Canada, approximately one in four women has osteoporosis.

Issue

The incidence of osteoporosis is rising, bisphosphonate use is increasing. Because of the costs involved, there is a need to assess the effectiveness of these drugs.

Methods and Results

We performed a systematic review to identify randomized controlled trials (RCTs) that compared postmenopausal women taking etidronate, alendronate, or risedronate to those on placebo. RCTs were categorized as primary or secondary prevention based on the absence or presence of pre-existing fractures. We meta-analyzed data from 11 etidronate RCTs (1,248 women), 11 alendronate RCTs (12,099 women), and six risedronate RCTs (13,795 women) to estimate the impact on fractures and adverse events. Seven RCTs were primary prevention trials. Additional analyses examined the influence of dose, duration, and baseline characteristics, including age on effect estimates.

Implications for Decision Making

- **Bisphosphonates have no demonstrated direct impact on clinically important fractures in primary prevention.** None of the bisphosphonates showed reductions in hip, wrist or other non-vertebral fractures. The effect of alendronate is limited to an observed reduced risk of radiographic vertebral fractures in one RCT. This surrogate outcome has been linked to excess morbidity and mortality.

- **Some bisphosphonates have a demonstrated direct impact on clinically important fractures in secondary prevention.** Alendronate and risedronate demonstrated reductions in risk of non-vertebral fractures. Both reduced risk of hip fractures, a major source of morbidity and mortality. Also, alendronate reduced the risk of wrist fractures. The demonstrated effect of etidronate is limited to a reduced risk of vertebral fractures.

- **The effect of bisphosphonates increases as postmenopausal women advance in age.** For alendronate, a projected 943 women aged 55 to 59 years would need to be treated to avoid a first hip fracture while 50 women aged 75 to 79 would need to be treated to avoid such a fracture.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Wells GA, Cranney A, Boucher M, Peterson J, Shea B, Robinson V, Coyle D, Tugwell P. *Bisphosphonates for the primary and secondary prevention of osteoporotic fractures in postmenopausal women: a meta-analysis.*

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EXECUTIVE SUMMARY

The Issue

The prevention of fractures associated with osteoporosis is a key public health issue in Canada. Osteoporosis is associated with medical, social, and financial implications, and its incidence is expected to increase significantly as the Canadian population ages. Several non-pharmacological and pharmacological interventions can lessen many of the consequences of osteoporosis. The oral bisphosphonate drugs (etidronate, alendronate, and risedronate) have been introduced as pharmacological options for the primary and secondary prevention of osteoporotic fractures. Since their entry into the Canadian market over five years ago, the use of these drugs has increased significantly. Given the resultant costs, there is a need to assess the clinical and cost-effectiveness of this drug class to determine if there is value in funding these drugs for primary and secondary prevention of osteoporotic fractures.

Objective

The aim of this systematic review was to assess the clinical effectiveness of etidronate, alendronate, and risedronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women receiving these agents, compared with untreated women, over a follow-up period of at least one year.

Methods

A systematic literature search of the evidence from randomized placebo-controlled trials of each of the three drugs was conducted, using accepted methodology for literature search, article selection, data extraction, and quality assessment. Clinical data analysis was also conducted according to accepted methodology for systematic reviews and meta-analyses. This report is modelled after three recently published reviews of etidronate, alendronate, and risedronate that were conducted, in part, by the authors of this report. The study selection, and data extraction and analysis were redone for this review.

Results

After reviewing the evidence for the oral bisphosphonates as therapeutic options for the primary and secondary prevention of osteoporotic fractures, it was found that etidronate has a beneficial effect on the reduction of vertebral fractures only when used for secondary prevention. The data do not support an effect of etidronate on the reduction of vertebral fractures when used for primary prevention or for reductions in non-vertebral, hip, or wrist fractures if used for primary or secondary prevention. Alendronate reduced the risk of vertebral, non-vertebral, hip, and wrist fractures when used for secondary prevention. There were no statistically significant reductions for the primary prevention of osteoporotic fractures by alendronate, with the exception of vertebral fractures. The data for risedronate support a beneficial effect in the reduction of risk of vertebral, non-vertebral, and hip fractures (but not for wrist), when it is used for secondary prevention. No estimates were possible for use of risedronate for primary prevention.

There were limitations to the data, in that the systematic review was not based on individual patient data, issues related to study quality were identified (i.e., lack of clarity of allocation concealment, large losses to follow-up), and the length of follow-up in the included trials was short. Comparisons of the adverse event potential of the drugs were complicated by the fact that the randomized controlled trials

that formed the basis of the meta-analyses tended to enrol healthier participants, and did not consistently report or measure rare events. Additionally, these trials were underpowered to detect differences in rare event rates, so it is difficult to make any conclusive statements about adverse drug events and the long-term tolerability of these drugs.

Conclusions

Overall evidence varies, depending on the bisphosphonate. For etidronate, most trials enrolled a small number of participants and were not necessarily designed to measure fractures, which limits our findings. Available evidence for alendronate and risedronate is more robust. Acknowledging the available evidence, we conclude that the main benefit of the three bisphosphonates available on the Canadian market for the management of osteoporotic fractures, is the secondary prevention of such fractures.

- Etidronate, used at 400 mg per day, demonstrated a main benefit in the secondary prevention of vertebral fractures. No statistically significant reductions in vertebral fractures were observed when it was used in primary prevention. No statistically significant reductions in non-vertebral, hip, or wrist fractures were found, whether etidronate was used for primary or secondary prevention.
- Alendronate demonstrated a main benefit in the secondary prevention of all osteoporotic fractures. At a dose of 10 mg per day, statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were observed. There were no statistically significant reductions found for the primary prevention of osteoporotic fractures, with the exception of vertebral fractures.
- Risedronate demonstrated a main benefit in the secondary prevention of most osteoporotic fractures. At a dose of 5 mg per day, statistically significant reductions in vertebral, non-vertebral, and hip fractures were observed (but not for wrist). Estimates of risk reductions for primary prevention were not possible, because only one trial was included in the review, and no fractures were observed.

ABBREVIATIONS

ADE	adverse drug events
AE	adverse events
ARR	absolute risk reduction
BMD	bone mineral density
CADRMP	Canadian Adverse Drug Reaction Monitoring Program
CI	confidence interval
DEXA	dual energy X-ray absorptiometry
DIN	drug identification number
FI	FRACTURE Index
FIT	fracture intervention trial
GI	gastrointestinal
HRT	hormone replacement therapy
N/A	not available
NA	not applicable
NE	not estimable
NNT	number needed to treat
RCT	randomized controlled trial
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
US	United States
WHO	World Health Organization
WMD	weighted mean difference
YSM	years since menopause

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APPENDICES – available from CADTH's web site www.cadth.ca

1 INTRODUCTION

1.1 Background

Osteoporosis is partly a natural consequence of aging.[1] This condition most often becomes clinically evident in adult women when they reach middle age or beyond; for this reason, it is often referred to as "postmenopausal osteoporosis."[2] The incidence of this disease is expected to increase significantly, because it is projected that approximately 25% of the Canadian population will be over the age of 65 years old by 2041.[3] In Canada, approximately one in four women, and one in eight men have osteoporosis.[3]

Osteoporosis is characterized by a decrease in the amount of bone to a level below that capable of maintaining the skeleton's structural integrity. The rate of bone formation is often normal, whereas the rate of bone resorption is increased.[2] The most notable complications of osteoporosis are fractures of the hip, wrist, and vertebrae. Age-related bone loss is the main cause of hip and vertebral fractures in elderly people.[1] Osteoporosis is described as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture," where "bone strength reflects the integration of two main features: bone density and bone quality."[3] The clinical indicator for bone quality is a patient's history of a fragility fracture. A fragility fracture is a fracture caused by an injury that would be insufficient to fracture normal bone (e.g., a fall from a standing height or less).[3] The preferred method of evaluating bone mass is the measurement of bone mineral density (BMD) of the spine and hip by dual energy X-ray absorptiometry (DEXA), which is also used to assess the response to therapy.[4]

The interpretation of BMD results is based on a comparison of a patient's BMD with the mean value for a young adult population of the same sex and race. The patient is assigned a "t-score," that is the number of standard deviations (SDs) above or below the mean BMD for normal young adults.[3] The World Health Organization (WHO) Study Group on Osteoporosis defines osteoporosis as "a hip BMD level of >2.5 SDs below the mean BMD for young, white, adult women."[5] According to this definition, approximately 30% of postmenopausal women have osteoporosis,[5,6] This definition does have limitations. The predictive value of BMD measurement for fracture varies depending on the site selected, the database for comparison, and the technology used. Furthermore, T-scores do not provide a good basis for establishing comparable diagnostic thresholds between sites and techniques.[7] As a result, between-site and between-technique variability introduces a potential for misclassification and unnecessary treatment of some individuals.

Osteoporosis can be detected by measurements of BMD, or inferred from the presence of pre-existing osteoporosis-related fractures. The presence of pre-existing osteoporotic fractures is a risk factor for future fractures. For example, among patients with osteoporosis (by BMD measurements but without pre-existing fractures) the three- to four-year incidence of new vertebral fractures ranges from 2% to 4%. In people with pre-existing osteoporotic fractures, the incidence increases to 15% to 29%. In the case of hip fractures, rates range from 1.1% to 5.1% in people with osteoporosis but without pre-existing fractures, and increases to 2.2% to 5.7% when pre-existing fractures are present.[1]

Reports show that 25% of women aged 80 years old have had ≥1 vertebral fracture.[8] Although some vertebral fractures are asymptomatic, Cauley *et al.*[9] have demonstrated excess mortality in women who have experienced a clinical vertebral fracture. The cumulative lifetime fracture risk for a 50-year-old woman with osteoporosis is as high as 60%.[10] As a result, effective fracture prevention would be expected to have an impact on morbidity and on mortality in these women.

Osteoporosis-related morbidity is associated with medical and social consequences.[3] The major source of morbidity and mortality from osteoporosis is attributed to hip fractures. Because of changing demographics, estimates suggest that the number of hip fractures in Canada will triple by 2040.[11] Hip fractures not only involve a short-term risk of mortality, but also present an impact on long-term function and independence. Among women who sustain a hip fracture, 50% do not return to their previous functional state, and become dependent on others for their daily activities.[3] A third of women who sustain a hip fracture will be discharged to nursing homes, and estimates suggest that the excess mortality associated with such fractures in older women may be as high as 20% in the first year.[9] The excess mortality may not be directly attributed to the hip fracture, and may be secondary to other underlying medical conditions.[12,13] Browner *et al*.[12] noted, in a prospective cohort of 9,198 elderly women, that there were 361 fractures of the hip or pelvis. However, 69% of deaths in these women, over a mean time period of two years, did not have a clear relationship to the fracture.

Osteoporosis is associated with a financial burden in Canada. The largest source of direct expenditures is attributed to the treatment of fractures and their sequelae. It is estimated that in 1993, the total acute care cost for osteoporosis (i.e., including hospitalization, ambulatory care, and drug therapy) was over C$1.3 billion.[3] In the US, it is estimated that these costs are between C$17 billion and C$20 billion per year.[3]

The prevention and treatment of osteoporosis are complex because of the multifaceted nature of the disease. Current approaches favour early intervention – from prevention to treatment of the disease – to ensure retention of bone mass, and to preserve the structural integrity of the skeleton and prevent fragility fractures. Although new treatments aimed at increasing bone formation, such as teriparatide,[14] are becoming available, most of the available osteoporosis drugs are anti-resorptive agents acting to decrease bone turnover. In Canada, these include the bisphosphonates: etidronate, alendronate, and risedronate. They are recommended as first-line preventive agents in postmenopausal women with low BMD, and as first-line agents for the treatment of postmenopausal women with osteoporosis.[3] Other pharmacological agents are available for the treatment of osteoporosis, including calcitonin, hormone replacement therapy (HRT), and raloxifene.[3] When this assessment was initiated, nasal calcitonin and HRT were considered second-line therapy options in the treatment of postmenopausal osteoporosis.[3] Raloxifene was considered to be first-line therapy in the prevention and treatment of postmenopausal osteoporosis.[3] A recent assessment determined, however, that raloxifene's main effect is a reduction in vertebral fractures in older postmenopausal women. This effect is offset by an increase in the rate of thromboembolic complications.[15] Consequently, these options are excluded from this review. Several non-pharmacological interventions have been recommended to prevent osteoporosis. These include taking the recommended daily amount of calcium and vitamin D; maintaining adequate dietary intake of protein; avoiding excessive caffeine and dietary sodium intake; and participating in physical activity.[3] The evaluation of these non-pharmacological interventions is beyond the scope of this review.

1.2 Overview of the Technology

Bisphosphonates are stable analogues of naturally occurring pyrophosphates. The mechanism of action of these drugs inhibits bone resorption through their effects on osteoclasts (i.e., cells associated with the absorption and removal of bone).[3] There are two classes of bisphosphonates: those that most closely resemble pyrophosphate (e.g., etidronate) and the more potent nitrogen-containing bisphosphonates (e.g., alendronate and risedronate).[3] Cyclical etidronate (in a 90-day-cycle package combination with calcium carbonate) was introduced in Canada in 1995;[1] single-entity alendronate was approved in 1998,[16] and risedronate was approved in 2000.[17]

All three agents are anti-resorptive, and marketed as interventions to reduce vertebral and non-vertebral fractures in postmenopausal women.[18] Etidronate has been shown to inhibit osteoclastic resorption.[19] It is given on a cyclical schedule every 90 days, because of its potential to impair bone mineralization when administered continuously for long periods.[3] Alendronate is administered daily or once weekly, depending on the formulation, and does not impair bone mineralization at doses that maximally inhibit bone resorption.[20] Similarly, risedronate is administered daily or weekly. These drugs have also been approved for use in other indications (e.g., treatment of Paget's disease, and treatment and prevention of corticosteroid-induced osteoporosis in men and women, as shown in Table 1).[21] These other indications are beyond the scope of this review. Generic versions of alendronate are commercially available in Canada. Etidronate is also available as a single entity, without calcium, under the trade name Didronel® for the treatment of Paget's disease and for hypercalcemia of malignancy.[21]

Tables 2 and 3 show the number of Canadian prescriptions dispensed, and the associated sales of these agents between 1999 and 2004. The use of bisphosphonates in Canada has increased, progressing from 1.5 million prescriptions dispensed in 1999, to 5 million in 2004 (Table 2). During the same period, the sales of bisphosphonates increased from C$98.6 million in 1999 to C$312.2 million in 2004 (Table 3). This represents a market expansion of >200% over five years.

In 1999, the bisphosphonate market in Canada was shared by two drugs: etidronate, with 49% of prescriptions and 35% of sales, and alendronate, with 51% of prescriptions and 65% of sales. Preparations were being made to launch risedronate in Canada. In 2004, etidronate ranked third, with 20% of prescriptions and 15% of sales; whereas alendronate led with 51% of prescriptions and 54% of sales. Risedronate affected the Canadian market shares; 29% of bisphosphonate prescriptions and 31% of sales in 2004 are attributed to this drug.

The results in Tables 2 and 3 represent all approved indications for the three drugs in Canada. It is reasonable to assume that most of the use and sales of bisphosphonates in Canada during this period was related to primary or secondary prevention, i.e., treatment of osteoporotic bone fractures. This is supported by restricted coverage of these agents for only these indications by government-sponsored drug programs in Canada, and by the use of the other approved indications in limited patient populations, such as those with Paget's disease (i.e., representing 1% to 2% of the general population).[2] Corticosteroid-induced osteoporosis is expected to affect only individuals with chronic inflammatory diseases (e.g., asthma or rheumatoid arthritis) requiring long-term systemic corticosteroids.[2] Etidronate is approved for the treatment of hypercalcemia of malignancy; this complication occurs in approximately 10% to 20% of patients with cancer. Other bisphosphonate drugs (e.g., pamidronate) used to treat this condition are usually administered in hospital; [22] oral etidronate can be used for 30 to 90 days to complete an injection treatment.[21] It is expected that the use of these agents in patients other than those with osteoporosis represents a small proportion of overall use.

Table 1: Bisphosphonates available in Canada for prevention and treatment of postmenopausal osteoporosis				
Generic Name	**Trade Name (manufacturer)**	**Dosing Recommendation***	**DIN†**	**Unit Cost per Tablet**
alendronate sodium	Fosamax® (Merck Frosst)	prevention: 5 mg daily; treatment: 10 mg daily or 70 mg once weekly	5 mg tablet 02233055; 10 mg tablet 02201011; 70 mg tablet 02245329	$1.70315[23] $1.755[24] $8.85[24]
alendronate sodium	Apo-Alendronate® (Apotex)	prevention: 5 mg daily; treatment: 10 mg daily or 70 mg once weekly	5 mg tablet 02248727; 10 mg tablet 02248728; 70 mg tablet 02248730	$1.13033[23] $1.1057[24] $5.5755[25]
alendronate sodium	Co-Alendronate (Cobalt Pharmaceuticals)	treatment: 70 mg once weekly	70 mg tablet 02258110	$5.5755[25]
alendronate sodium	Gen-Alendronate (Genpharm Inc.)	prevention: 5 mg daily; treatment: 10 mg daily	5 mg tablet 02270110; 10 mg tablet 02270129	$1.19255[23] $1.1057[26]
alendronate sodium	Novo-Alendronate® (Novo-Pharm)	prevention: 5 mg daily; treatment: 10 mg daily or 70 mg once weekly	5 mg tablet (02248251) 10 mg tablet (02247373) 70 mg tablet 02261715	$1.13033[23] $1.1057[24] $5.5755[25]
alendronate sodium	PMS-Alendronate® (Pharmascience)	treatment: 70 mg once weekly	70 mg tablet (02273179)	$5.575[27]
alendronate sodium	RIVA-Alendronate (RIVA Lab Inc.)	treatment: 70 mg once weekly	70 mg tablet (02270889)	not listed‡
etidronate disodium and calcium carbonate	Didrocal® (Procter & Gamble)	prevention or treatment: 90-day cycle, etidronate 400 mg daily x 14 days, then calcium carbonate 1,250 mg daily x 76 days	02176017	$ 0.4077[24]
risedronate	Actonel® (Procter & Gamble)	prevention: 5 mg daily; treatment: 5 mg daily or 35 mg once weekly	5 mg tablet: 02242518 35 mg tablet: 02246896	$1.66[24] $8.85[24]

*Source: Compendium of Pharmaceutical Specialities (CPS) 2004;[21] †Source: Health Canada – Drug Product Database (DPD) – Active products;[28] ‡not listed in any of the online publicly funded formularies.; DIN=drug identification number.

Table 2: Estimated number of bisphosphonate prescriptions in Canada* 1999 to 2004						
Bisphosphonate (trade name)	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
etidronate (Didrocal®)	735,118	941,730	1,073,185	1,125,072	1,102,139	1,010,611
alendronate (all brands)	753,337	948,109	1,088,320	1,368,857	2,089,382	2,552,442
(Fosamax®)	753,337	948,109	1,108,320	1,368,857	2,052,759	2,439,440
(Novo®-Alendronate)	N/A	N/A	N/A	N/A	36,623	106,176
(Apo®-Alendronate)	N/A	N/A	N/A	N/A	N/A	6,826
risedronate (Actonel®)	56	12,654	256,242	612,675	981,322	1,443,029
Total	**1,488,511**	**1,902,493**	**2,417,747**	**3,106,604**	**4,172,843**	**5,006,082**

*Source: IMS Health Canada, CompuScript.; N/A=not available.

Table 3: Estimated sales of bisphosphonates in Canadian retail pharmacies* 1999 to 2004						
Bisphosphonate (trade name)	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
etidronate (Didrocal®)	$34,9	$44,7	$50,1	$52,3	$51,0	$46,8
alendronate (all brands)	$63,7	$79,4	$90,9	$109,3	$143,8	$168,4
(Fosamax®)	$63,7	$79,4	$90,9	$109,3	$141,0	$160,3
(Novo® Alendronate)	N/A	N/A	N/A	N/A	$2,8	$7,6
(Apo® Alendronate)	N/A	N/A	N/A	N/A	N/A	$0.5
risedronate (Actonel®)	$0,01	$1,7	$22,2	$50,9	$71,7	$97,0
Total	**$98,6**	**$125,8**	**$163,2**	**$212.5**	**$266.5**	**$312,2**

*Source: IMS Health Canada, CompuScript; estimated prescription costs, including professional fees (C$ million).; N/A=not available.

2 THE ISSUE

The prevention of fractures associated with osteoporosis is a public health issue in Canada. The incidence of osteoporosis is expected to increase significantly as the Canadian population ages (i.e., 25% of the population will be >65 years old by 2041). The condition affects women and men, to different degrees, and the management of these patients is associated with medical, social, and financial implications. The medical complications of hip (mainly), wrist, and vertebral fractures cause significant morbidity and mortality. Among women who sustain a hip fracture, 50% become

dependent on others for their daily activities; a third of women are discharged to nursing homes, and for older women, excess mortality in the first year may be as high as 20%. The financial burden is significant. Many consequences of osteoporosis are potentially lessened through the use of non-pharmacological and pharmacological interventions. One pharmacological intervention is the oral bisphosphonate class of drugs. The use of these drugs has increased significantly since they entered the Canadian market, with sales of bisphosphonates exceeding C$300 million in 2004. Given the cost of these agents, there is a need to assess the clinical and cost-effectiveness of this drug class, to aid decision makers in determining if there is value in funding these drugs for the primary and secondary prevention of osteoporotic fractures.

3 OBJECTIVES

The objective of this systematic review is to assess the clinical effectiveness of the bisphosphonates (etidronate, alendronate, and risedronate) in the primary and secondary prevention of osteoporotic fractures. The stated objectives were to assess the effectiveness in the primary and secondary prevention of osteoporotic fractures in postmenopausal women receiving:

- etidronate, compared to those women receiving placebo or calcium or vitamin D, with a follow-up of >1 year for the outcome of fracture incidence
- alendronate, compared to those women receiving placebo or calcium or vitamin D, with a follow-up of >1 year for the outcome of fracture incidence
- risedronate, compared to those women receiving placebo or calcium or vitamin D, with a follow-up of >1 year for the outcome of fracture incidence.

A separate CADTH report will evaluate the cost-effectiveness of these three drugs and teriparatide, primarily for the secondary prevention of osteoporotic fractures in elderly women.

4 CLINICAL REVIEW

4.1 Methods

A systematic review and analysis of clinical data was conducted using the Cochrane Collaboration methodology, as described in the Cochrane Handbook.[29]

4.1.1 Literature search strategy

The literature search was guided by the Cochrane Collaborative approach for identifying randomized controlled trials (RCTs), as described by Dickersin *et al.*,[30] and modified for the Cochrane Musculoskeletal Group. We searched MEDLINE® from 1966 to November 2004, Current Contents®, the Cochrane Controlled Trials Register, and citations of relevant articles. No language restrictions were applied to the search strategy. We used the name of the drug [i.e., etidronate (Didronel®, coherence therapy), alendronate, and risedronate] and the following key and text words: bisphosphonates, diphosphonates, osteoporosis, and postmenopausal (Appendices 1 to 3). Two reviewers examined each title generated from the search, identified potentially eligible articles, and obtained the abstracts. The full article text was obtained for abstracts consistent with study eligibility. We only considered studies for inclusion if the findings were published as a full article or as an abstract.

The literature search was conducted in two stages. The first stage was the basis for our systematic reviews published from 2001 to 2002,[31-33] then we updated the search. For the etidronate review, the first search for 1966 to 1998 included MEDLINE®, Current Contents®, and hand searching of conference abstracts (e.g., Osteoporosis International, Journal of Bone and Mineral Research). This was followed by a MEDLINE® search for 1998 to November 2004. For the alendronate review, the first search for 1966 to 1999 included MEDLINE®, EMBASE®, Current Contents®, and the Cochrane Controlled Trials Register followed by a MEDLINE® search for 1999 to November 2004. For the risedronate review, the first search for 1966 to December 2000 included MEDLINE®, EMBASE®, Current Contents®, the Cochrane Controlled Trials Register, and hand searching of conference abstracts and Food and Drug Administration (FDA) proceedings. This was followed by a MEDLINE® search for 2000 to November 2004.

4.1.2 Selection criteria and method

Trials that satisfied the following criteria were included.

a) Study design

RCT had to have a duration of >1 year.

b) Population group

The population group was postmenopausal women. Primary and secondary prevention trials were accepted. We used a hierarchy to define primary versus secondary prevention according to the information available. We selected a definition of primary and secondary prevention that gave more weight to study inclusion criteria than baseline statistics. If the inclusion criteria restricted the population to women whose bone density was >2 SD values below the peak bone mass, or the inclusion criteria restricted the population to women that had experienced previous vertebral compression fractures, the trial was considered a secondary prevention study. If such inclusion criteria were not provided, the baseline statistics were considered as follows. We considered the trial as primary prevention if the average t-score and SD included women whose bone density was <2 SD of the mean, or if the prevalence of vertebral fracture at baseline was <20%. When these data were unavailable, we considered a trial as secondary prevention, if the average age was >62 years old.

c) Intervention

Etidronate, alendronate, or risedronate were the interventions.

d) Comparators

The comparator was no treatment, including placebo or calcium or vitamin D. If the study used calcium or vitamin D controls, these treatments would have to be given concurrently in the bisphosphonate treatment groups.

e) Outcomes

The outcome was incidence of fractures, including vertebral, non-vertebral, hip, and wrist fractures.

4.1.3 Data abstraction strategy

Two independent reviewers abstracted all information and data using standardized data abstraction forms, and a third reviewer verified the data. Abstraction included information on pertinent methodological aspects of the study design, characteristics of the participants, the specific dose of the study drug used, and the outcomes assessed (e.g., number of vertebral, non-vertebral, hip, and wrist fractures). All reported fractures, clinical or radiographic, were considered for fracture data. For details of the data extraction form that was used, please refer to Appendix 4.

For the yearly data, our unit of analysis was the number of patients sustaining a fracture. If an article reported yearly data, we used the time points available. We used the same baseline denominator for each time point. For follow-up denominators, we used any yearly follow-up number of patients reported in the article, if available. If these were unavailable, we assumed a uniform drop-out rate for each year, and calculated the denominators by determining the proportion of subjects that would have remained at the end of the year in question, based on the number of withdrawals over the course of the study. If an article reported only end-of-study outcomes, these were used for our analysis with the exception of outcomes where the numerator was zero for both treatment groups. In these instances, we included the outcome, with any necessary adjustments for follow-up denominators, for the earlier years in the duration of the study. For example, if a trial reported zero hip fractures for both treatment arms at the end of year 3, we would also include zero hip fractures for that trial at years 1 and 2 in our analysis.

The number of fractures was used as the unit of analysis for person-year data if it was available. In most cases, these data were unavailable, so we used the number of women sustaining a fracture. For denominators, we multiplied the number of women followed by the length of the study. For radiographic vertebral fractures, we used the number of women with available radiographs, if the number was reported in the article. For clinical fractures, we estimated the number of women followed during the study, by taking the mean of the baseline and follow-up denominators.

4.1.4 Strategy for quality assessment

Two reviewers assessed each eligible RCT, using the quality assessment form provided in Appendix 5. Quality assessment was based on allocation concealment as considered by the Cochrane Collaboration. Research has shown that a lack of adequate allocation concealment is associated with bias,[29] and studies can be judged on the method of allocation concealment. The method for assigning participants to interventions should be robust against patient and clinician bias, and its description should be clear. The reviewers were required to indicate whether allocation concealment was adequate (A), unclear (B), or inadequate (C). The Cochrane Collaboration's criteria for making this judgment are as follows:

a) Adequate

The following are some approaches that can be used to ensure adequate concealment schemes: centralized or pharmacy-controlled randomization; pre-numbered or coded identical containers administered serially to participants; on-site computer system combined with allocations kept in a locked, unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered; or sequentially numbered or sealed, opaque envelopes. Other similar approaches could be included if the person who generated the allocation scheme did not administer it.

b) Inadequate

Approaches to allocation concealment that are considered inadequate include alternation; use of case record numbers dates of birth or day of the week; and any procedure that is transparent before allocation, such as an open list of random numbers.

c) Unclear

When studies do not report any concealment approach, adequacy should be considered to be unclear. Examples include stating that a list or table was used; only specifying that sealed envelopes were used; and reporting an apparently adequate concealment scheme in combination with other information that leads the reviewer to be suspicious.

4.1.5 Data analysis methods

We calculated the relative risk (RR) for the analysis of vertebral, non-vertebral, hip, and wrist fractures, using the methods for pooling the results described by Fleiss.[34] The pooled or weighted RRs using the general inverse variance method for the weights were calculated. For the pooled results, site-specific 95% confidence intervals (CIs) were calculated for vertebral, non-vertebral, hip, and wrist fractures. We tested for association using a chi-square test procedure, taking $p<0.05$ to show the presence of statistical association. We also tested for homogeneity using a chi-square test procedure, taking the specific cut-off for presence of statistical heterogeneity as $p=0.10$.[34]

If the relative risk reduction (RRR) was significant ($p<0.05$), then the absolute risk reduction (ARR) and number needed to treat (NNT) were calculated. For these calculations, the five-year risk of fracture in the untreated population was based on the FRACTURE Index (FI) of Black *et al.,*[35] and the lifetime and five-year age-specific risks in the untreated population were based on the model by Doherty *et al*.[36] for predicting osteoporotic fractures in postmenopausal women (Appendices 37a, 37b, 37c, and 38).

Trials varied in length of treatment (e.g., one to four years), and the number of patients available for study at the start of treatment (i.e., baseline denominator), compared to those available at different points during the trial (i.e., follow-up denominators). For time points when fracture data were available and the number of patients was not stated, follow-up denominators were interpolated using the baseline and end-of-study denominators, assuming a uniform loss to follow-up. The base case used for the review of fractures considered the data available for the longest period of time for the treatment in the trial (i.e., "all years"), and used the baseline denominators for the number of patients in the trial.

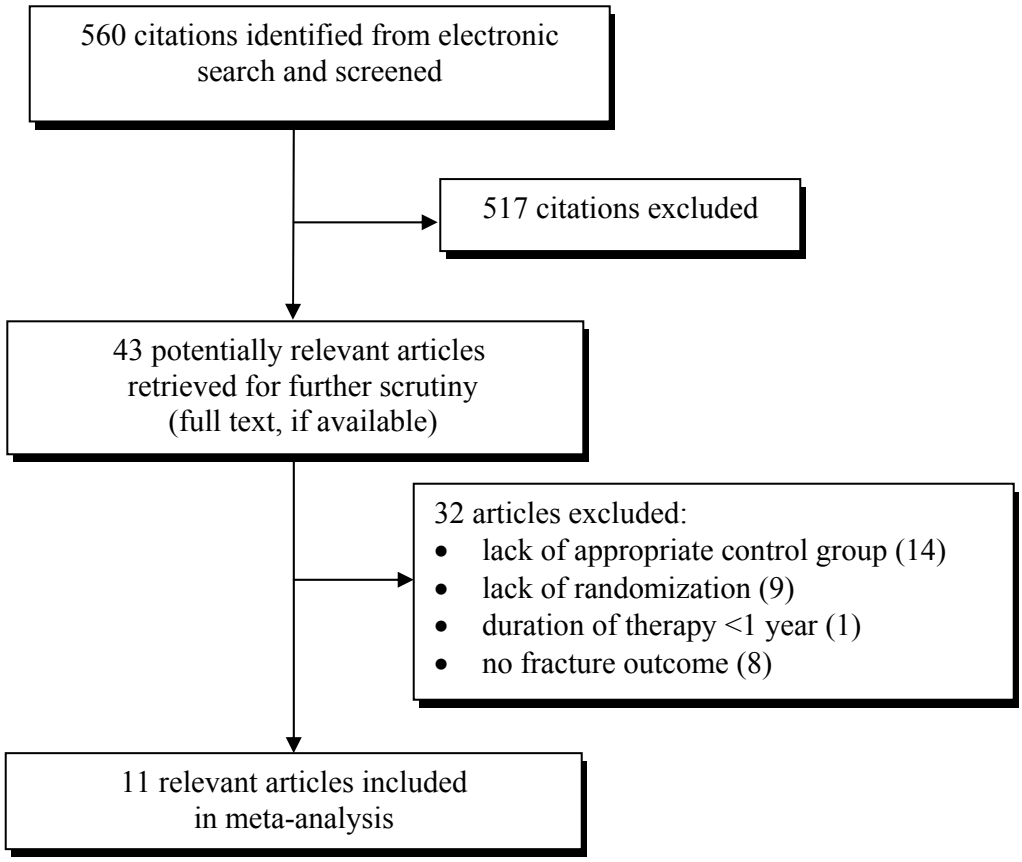
Data were initially pooled broadly across primary and secondary trials. The overall analysis was also considered using person-years of observation. We also conducted subgroup analysis for primary versus secondary, treatment duration, and dose. Furthermore, we conducted sensitivity analysis for baseline denominators versus follow-up denominators, fixed versus random effects model, and baseline vertebral fracture rate. For the last sensitivity analysis, recall that the vertebral fracture criteria for a trial to be considered as secondary prevention was a prevalence of vertebral fracture at baseline of >20%. A sensitivity analysis using different vertebral fracture rates (i.e., 100%, >80%, >60%, >40%, >20%) without the BMD and age criteria was conducted. This allowed us to evaluate whether the effect of bisphosphonates on the secondary prevention of osteoporotic fractures varied, depending on how strictly secondary prevention was defined.

4.2 Results for Etidronate

4.2.1 Quantity of research available

The literature search revealed 560 citations (Figure 1). Of these, 43 articles were retrieved for further scrutiny.[19,37-78] A total of 32 articles were excluded for various reasons, including lack of an appropriate control group,[38,41,43,45,49,50,53,55-57,60,63,65,73] lack of randomization,[39,51,59,62,66,67,70,72,75] study duration <1 year,[46] and no fracture outcome reported.[37,40,42,44,47,54,76,77] Eleven trials [19,48,52,58,61,64,68,69,71,74,78] met all the selection criteria.

Figure 1: Literature search for etidronate



4.2.2 Trial characteristics

The characteristics of the 11 selected trials are shown in Table 4. Of the 1,248 women enrolled in the trials, 624 received placebo. Eight trials included women with established osteoporosis; these were classified as secondary prevention trials.[19,52,58,64,68,71,74,78] The remaining three were classified as primary prevention trials.[48,61,69]

We excluded data from the HRT treatment arm or combined HRT and etidronate arm of the study by Wimalawansa.[78] One study[19] included four treatment groups; two of these were placebo groups. This study was analyzed as two studies (i.e., Watts A, and Watts B). In Watts A, cyclical etidronate is compared with placebo; whereas in Watts B, cyclical etidronate and phosphate are compared with placebo and phosphate. Because we divided the Watts study in two, we consider the analysis of fracture data reported in the following tables to come from a possible total of 12 trials.

Concealed allocation was unclear for all 11 trials. Seven trials[19,48,52,61,64,69,78] had a loss to follow-up from 5% to 20%, three trials[58,68,74] were over 20%, and one trial[71] did not report the loss to follow-up.

Table 4: Characteristics of selected studies for etidronate						
Trial (primary or secondary prevention)*	**Number of Patients (treatment/ control)**	**Mean Age (SD), Years Since Menopause (SD), Baseline Calcium Intake/day (SD), Lumbar BMD g/cm^2, T-score,† Prevalent Vertebral Fractures**	**Intervention; [days off txt]; (concurrent calcium or vitamin D supplements)**	**Study Length (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Herd (primary)	152 (75/77)	age: 54.8 (4.9); YSM: 5.5 (2.9); calcium: not reported; BMD: 0.84 g/cm^2; T-score: −1.9; fractures: 0% (excluded)	etidronate 400 mg/day versus placebo; [76 days]; (500 mg calcium /day)	2	vertebral (lateral radiographs of thoracic and lumbar spine at baseline and 24 months)	etidronate: 11/75 (14.6%); placebo: 6/77 (7.8%); total:17/152 (11.2%)
Ishida (secondary)	132 (66/66) (other txt reported but not included: HRT, calcitonin, vitamin K, alfacalcidol)	age: 69 (13); YSM: 19.5; calcium: not reported; BMD distal radius: 0.44 (0.09); T-score: 65% of young adult's score; fractures: 31%	etidronate 200 mg/day versus no treatment; [70 days]; (no concurrent therapy reported)	2	vertebral, hip, wrist	etidronate: 6/66 (9.1%); control: 4/66 (6.1%); total: 10/132 (7.6%)
Lyritis (secondary)	100 (50/50)	age: 72.0 (0.4); YSM: 25.8 (1.7); calcium: 522 mg (48); BMD: 0.57g/cm^2; T-score: −4.3; fractures: 100%	etidronate 400 mg/day versus control; [65 days]; (500 mg calcium/day and 2 *u*g calcitriol x 5 days before cycle)	4	vertebral, non-vertebral, hip, wrist	etidronate: 11/50 (22%); control: 15/50 (30%); total: 26/100 (26.0%)
Meunier (primary)	54 (27/27)	age: 52.7 (4.0); YSM: 2.4 (1.8); calcium: 876 mg (559); BMD: 0.90 g/cm^2; T-score: −1.3; fractures: not reported	etidronate 400 mg/day versus placebo; [77 days]; (500 mg calcium/day)	2	vertebral, non-vertebral	etidronate: 2/27 (7.4%); placebo: 3/27 (11.1%); total: 5/54 (9.3%)

Table 4: Characteristics of selected studies for etidronate						
Trial (primary or secondary prevention)*	**Number of Patients (treatment/ control)**	**Mean Age (SD), Years Since Menopause (SD), Baseline Calcium Intake/day (SD), Lumbar BMD g/cm^2, T-score,† Prevalent Vertebral Fractures**	**Intervention; [days off txt]; (concurrent calcium or vitamin D supplements)**	**Study Length (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Montessori (secondary)	80 (40/40)	age: 62.5 (6.2); YSM: 14.9 (6.1); calcium: 874 mg; BMD: 0.67 g/cm^2; T-score: −3.4; fractures: 29%	etidronate 400 mg/day versus control; [76 days]; (500 mg calcium/day)	3	vertebral, non-vertebral	etidronate (2 years): 0/40 (0%); control (2 years): 6/40 (15%); total (3 years): 16/80 (20%)
Pacifici (secondary)	57 (30/27), HRT group (n=36) not included	age: 61 (7.8); YSM: 13.8 (9.5); calcium: 875 mg/day (406); QCT: 79.1 mg/cm^3 (26.3); 100% had fractures or evidence of demineralization on QCT	etidronate 400mg/day with 7.5 g K phosphate/cycle versus control; [56 days]; (1 g calcium /day)	2	vertebral	etidronate: 14/30 (46.7%); control: 12/27 (44.4%); total: 26/57 (46%)
Pouilles (primary)	109 (54/55)	age: 53.8 (3.1); YSM: 2.6 (1.4); calcium: not reported; BMD: 0.96 gm/cm^2 ; T-score: −0.8; fractures: not reported	etidronate 400 mg/day versus placebo; [77 days]; (500 mg calcium/day)	2	vertebral, non-vertebral	etidronate: 9/54 (16.7%); placebo: 9/55 (16.4%); total: 18/109 (16.5%)
Shiota (secondary)	40 (20/20)	age: 61.7; YSM: 14.6 (7.8); calcium: not reported; BMD: 0.56 (0.08); T-score: −4.3; fractures: 60% (patients with fractures at L2 to 4 excluded)	etidronate 200 mg/day versus control; [70 days]; (2 g calcium/day and 0.5 ug alfacalcidol/day)	2	vertebral	withdrawals not reported
Storm (secondary)	66 (33/33)	age: 68.3 (7.3); YSM: 21.6 (10.2); calcium: not reported; BMD: 25.1 g (7.3); fractures: 100%	etidronate 400 mg/day versus placebo; [91 days]; (500 mg calcium /day and 400 IU vitamin D daily)	3	vertebral (for person-years only), non-vertebral, hip, wrist	etidronate: 13/33 (39.4%); placebo: 13/33 (39.4%); total: 26/66 (39.4%)

Table 4: Characteristics of selected studies for etidronate						
Trial (primary or secondary prevention)*	**Number of Patients (treatment/ control)**	**Mean Age (SD), Years Since Menopause (SD), Baseline Calcium Intake/day (SD), Lumbar BMD g/cm^2, T-score,† Prevalent Vertebral Fractures**	**Intervention; [days off txt]; (concurrent calcium or vitamin D supplements)**	**Study Length (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Watts (secondary)	423 (212/211)	age: 65.1 (13); YSM: 17.9 (16.5); calcium: 746 mg/day (782); BMD: 0.86 g/cm^2 ; T-score: −1.7; fractures: 100%	etidronate 400 mg/day, placebo, etidronate 400 mg/day with 3 g phosphorous, placebo with 3 g phosphorous; [91 days]; (500 mg calcium /day)	2	vertebral, non-vertebral, hip, wrist	etidronate: 27/212 (12.7%); placebo: 33/211 (15.6%); total: 60/423 (14.2%)
Wimalawansa (secondary)	35 (17/18), HRT group (n=37) not included	age: 64.9 (7.8); YSM: 15.1 (6.8); calcium: 696 mg (339); BMD: 0.83 g/cm^2; T-score: −2.0 ; fractures: 100%	etidronate 400 mg/day versus control; [84 days]; (1 g calcium/day and 400 IU vitamin D daily)	4	vertebral; non-vertebral	etidronate: 3/17 (17.6%); control: 4/18 (22.2%); total: 7/35 (20.0%)

*Refers to a priori definition of treatment and prevention; †t-score calculated using lumbar spine BMD [(LS BMD −1.047)/0.110]; YSM=years since menopause; BMD=bone mineral density; txt=treatment; HRT=hormone replacement therapy; K=potassium; QCT=quantitative computerized tomography.

4.2.3 Data analysis and synthesis

a) Effect on fractures

Table 5 shows a review of fractures for the standard dose of etidronate (400 mg), using the data available for the longest treatment duration in the trials, and using the baseline denominators for the number of patients in the trial (i.e., base case). In general, the pooled estimate of RR of fracture after treatment with etidronate was not significant for non-vertebral, hip, and wrist fractures, whether it was used for primary or secondary prevention. For vertebral fractures, the pooled estimate of the RR was significant for secondary prevention, but not for primary prevention.

Table 5: Weighted RR of fracture after etidronate (400 mg)

Fracture Sites	Primary or Secondary Prevention	Number of Trials	Number of Participants (treatment/ control)	RR (95% CI)	Association p value	Heterogeneity p value
vertebral	overall	8	430/428	0.59 (0.36; 0.96)	0.03	0.70
	primary	2	81/82	3.03 (0.32; 28.44)	0.3	0.99
	secondary	6	349/346	0.53 (0.32; 0.87)	0.01	0.77
non-vertebral	overall	7	393/394	0.98 (0.68; 1.42)	0.9	0.87
	primary	2	81/82	0.56 (0.20; 1.61)	0.3	0.81
	secondary	5	312/312	1.07 (0.72; 1.60)	0.7	0.88
hip	overall	4	295/294	1.20 (0.37; 3.88)	0.8	0.53
	primary	0	N/A	N/A	N/A	N/A
	secondary	4	295/294	1.20 (0.37; 3.88)	0.8	0.53
wrist	overall	4	295/294	0.87 (0.32; 2.36)	0.8	0.51
	primary	0	NA	NA	NA	NA
	secondary	4	295/294	0.87 (0.32; 2.36)	0.8	0.51

RR=relative risk; CI=confidence interval; N/A=not applicable.

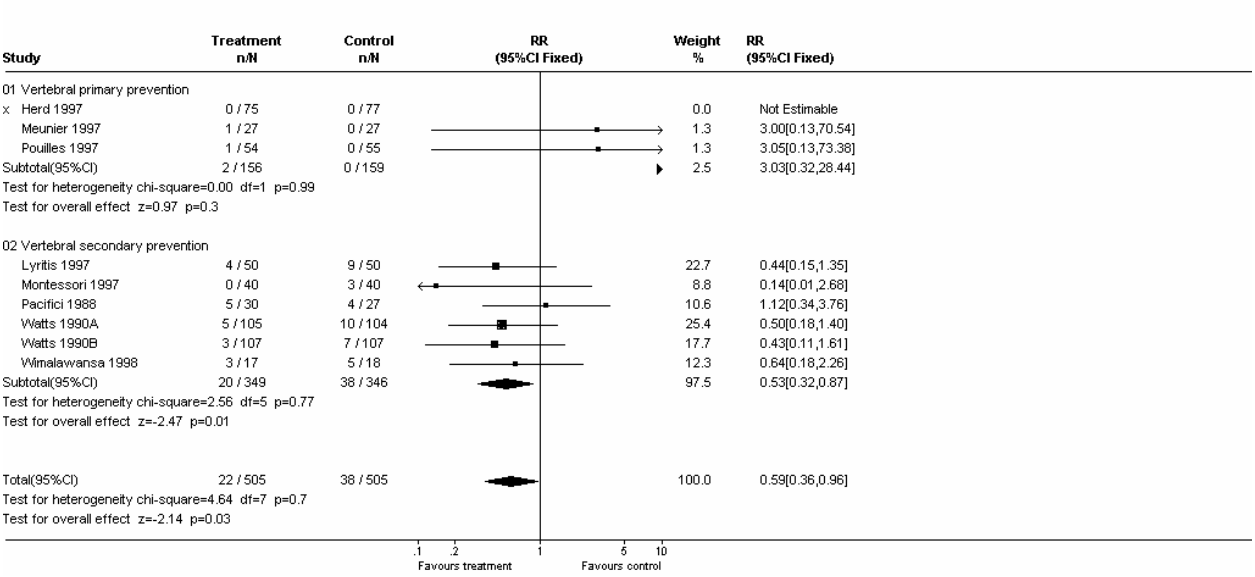
Vertebral fractures

Vertebral fractures were reported in all 11 trials. Two of these trials[52,71] used a non-standard dose of 200 mg, and were later considered in the section on subgroup analysis. One trial[74] reported results in person-years only. The Watts[19] trial was considered to consist of two studies. As a result, we considered the eight trials reporting vertebral fractures corresponding to the standard 400 mg dose. One trial reported that no fractures occurred in either treatment group.[48]

The pooled estimate of the RR of vertebral fractures from the eight trials that could be analyzed resulted in a significant 41% reduction in vertebral fractures [RR 0.59 (95% CI: 0.36; 0.96)] (Table 5 and Figure 2). This demonstrates a fracture risk reduction with etidronate; results are consistent across the eight trials (p=0.70).

The significance in the overall RR of vertebral fractures was due to the six secondary prevention trials that demonstrated a significant RRR of 47% in vertebral fractures [RR 0.53 (95% CI: 0.32; 0.87)], compared to the pooled result for the two primary prevention trials [RR 3.03 (95% CI: 0.32; 28.44)], which was not significant.

Figure 2: RR of vertebral fracture after etidronate (400 mg)



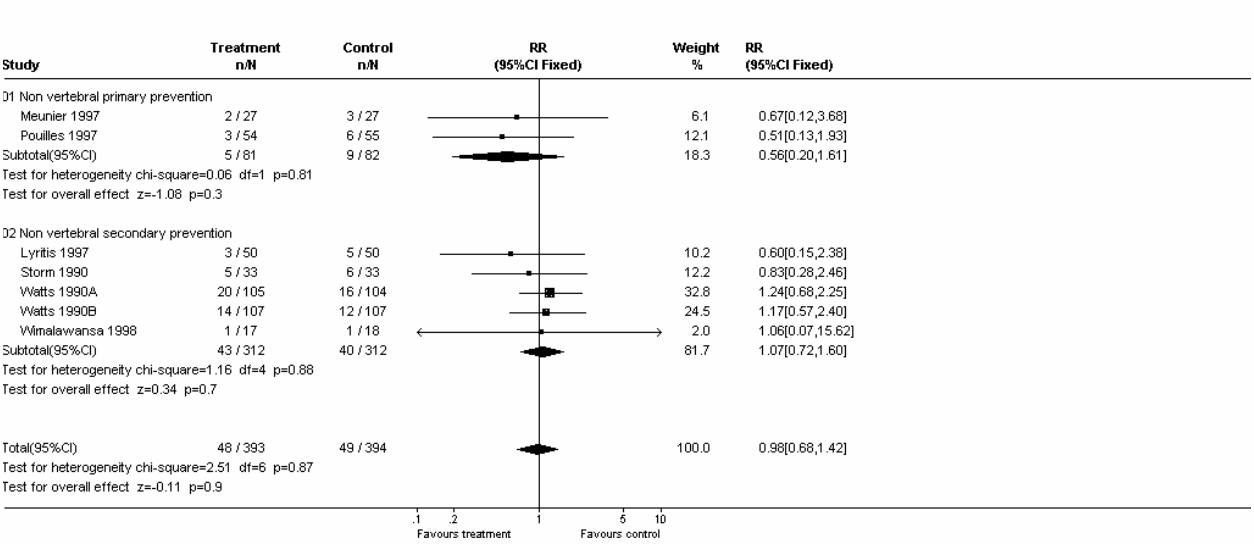
Corresponding to the significant RRR of 47% for the secondary prevention of vertebral fractures, the absolute measures ARR and NNT of the five-year risk of vertebral fracture after treatment with etidronate were calculated for different levels of increasing risk, as measured by the FI. Results are provided in Appendix 6 and for increasing age in Appendix 7. For the illustrative case of the patient with an FI of six to seven, the ARR in vertebral fracture was 3.3% (i.e., a reduction in risk from 7.1% to 3.8%), and the NNT was 30 (i.e., 30 patients would need to be treated to avoid one vertebral fracture). Across the range of increasing FI risk, the ARR for vertebral fracture ranged from 0.6% to 5.3%, and the NNT, to avoid one vertebral fracture, ranged from 167 to 19. For the illustrative patient in the age group 60 to 64 years old, the ARR for the first vertebral fracture was 0.5% (i.e., a reduction in risk from 1.0% to 0.5%), and the NNT was 213 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 4.6% (i.e., a reduction in risk from 9.7% to 5.1%), and the NNT was 22 patients treated to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first vertebral fracture increased from 0.1% for the youngest age group (50 to 54 years old) to 2.2% in the highest age group (90+ years old). The NNT decreased from 1,064 to 45. For the subsequent fracture, ARR increased from 0.2% to 13.1%, and the NNT decreased from 426 to eight.

Non-vertebral fractures

Non-vertebral fractures were reported in seven trials.[19,58,61,69,74,78] The lack of effect of etidronate on non-vertebral fractures is shown in Table 5 and Figure 3. The 95% CI around the RR estimate for all non-vertebral fractures was wide, with an RRR of approximately 32%, and an RR increase of 42% [RR 0.98 (95% CI: 0.68; 1.42)]. Results were consistent across the seven trials (p=0.87).

A similar lack of effect of etidronate on non-vertebral fractures was found for primary and secondary prevention trials. Pooled results for both primary prevention trials [RR 0.56 (95%CI: 0.20; 1.61)] and the five secondary prevention trials [RR 1.07 (95% CI: 0.72; 1.60)] were not significant.

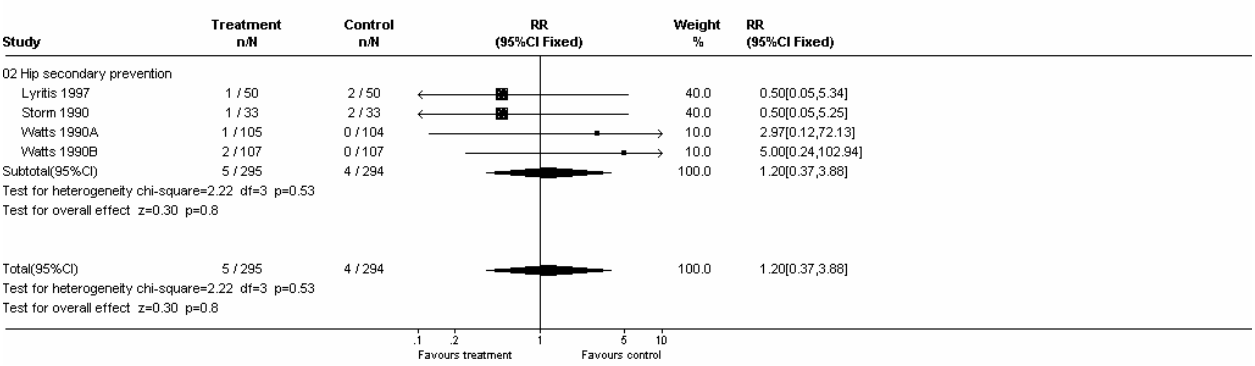
Figure 3: RR of non-vertebral fracture with etidronate (400 mg)



Hip fractures

Hip fractures were reported in four trials.[19,58,69,74] Results of the pooled hip-fracture data [RR 1.20 (95% CI: 0.37; 3.88)] were not significant (Table 5 and Figure 4). All four trials investigated secondary prevention.

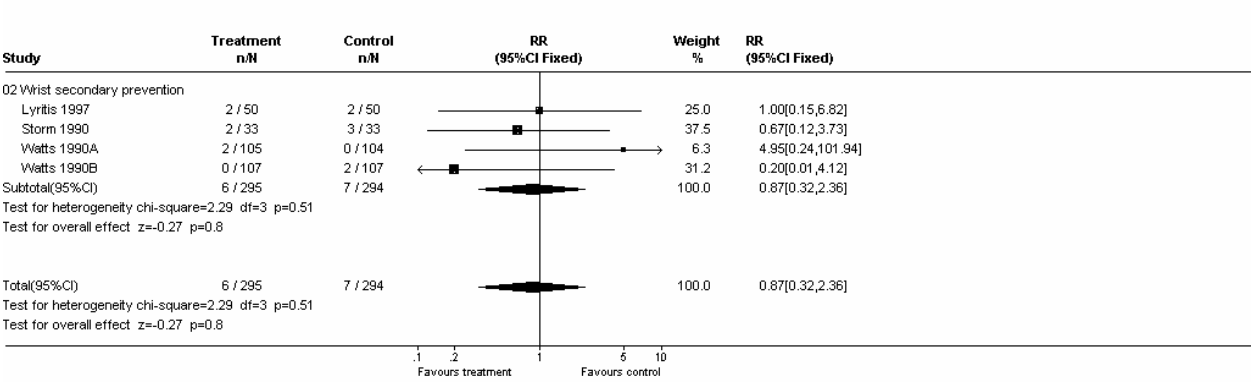
Figure 4: RR of hip fracture after etidronate (400 mg)



Wrist fractures

Wrist fractures and hip fractures were reported in the same four secondary prevention trials.[19,58,69,74] Results for the pooled wrist-fracture data [RR 0.87 (95% CI: 0.32; 2.36)] (Table 5 and Figure 5) were not significant.

Figure 5: RR of wrist fracture after etidronate (400 mg)



b) Additional analyses

Person-years

Similar results are found for vertebral, non-vertebral, hip, and wrist fractures using person-years (Table 6). The pooled result for vertebral fractures was not significant for the two primary prevention trials; for the six secondary prevention trials, a significant 55% reduction in vertebral fractures [RR 0.45 (95% CI: 0.31; 0.64)] was found, with results consistent across the secondary trials (p=0.40).

Table 6: Weighted RR of fracture with etidronate (400 mg) in person-years

Fracture Sites	Primary or Secondary Prevention	Number of Trials	Number of Participants (treatment/ control) person-years	RR (95% CI)	Association p value	Heterogeneity p value
vertebral	overall	8	972/896	0.48 (0.34; 0.68)	<0.0001	0.37
	primary	2	151/152	3.00 (0.32; 28.50)	0.3	0.99
	secondary	6	821/744	0.45 (0.31; 0.64)	<0.0001	0.40
non-vertebral	overall	5	821/780	0.95 (0.65; 1.40)	0.8	0.61
	primary	2	151/152	0.56 (0.19; 1.63)	0.3	0.83
	secondary	3	670/628	1.04 (0.68; 1.58)	0.9	0.47
hip	overall	3	670/628	1.14 (0.34; 3.90)	0.8	0.28
	primary	0	N/A	N/A	N/A	N/A
	secondary	3	670/628	1.14 (0.34; 3.90)	0.8	0.28
wrist	overall	3	670/628	0.80 (0.27; 2.37)	0.7	0.96
	primary	0	N/A	N/A	N/A	N/A
	secondary	3	670/628	0.80 (0.27; 2.37)	0.7	0.96

RR=relative risk; CI=confidence interval; N/A=not applicable.

Subgroup analysis

Treatment duration: No trends were found for years of treatments that deviated from the overall RR estimates (Appendix 8).

Treatment dose: A 200 mg dose of etidronate was used in two secondary prevention trials.[52,71] Results were available for two years of treatment. For the base case, we found a significant reduction (68%) in vertebral fractures [RR 0.32 (95% CI: 0.16; 0.64)], a non-significant reduction in hip fractures [RR 0.33 (95% CI: 0.01; 8.04)], and a non-significant reduction in wrist fractures [RR 0.50 (95% CI: 0.05; 5.38)]. Similar results were obtained using person-years. Results were consistent with those for the standard 400 mg dose, with significance demonstrated only for vertebral fractures.

Sensitivity analysis

Baseline versus follow-up denominators: Using the data available for longest treatment duration, standard dose of etidronate (400 mg), and follow-up denominators for the number of patients in the trials, we prepared a summary of the review of fractures (Appendix 9). These data are provided by years of treatment in Appendix 10. Pooled estimates of the RR of fracture after etidronate were similar to those obtained using the baseline denominators.

Random versus fixed effects model: There was no instance where heterogeneity of the trial results necessitated using a random effects model. Results obtained using the random and fixed effects were similar.

Baseline vertebral fracture rate: Using different baseline vertebral fracture rates (i.e., 100%, >80%, >60%, >40%, >20%) for defining secondary prevention trials, we prepared a summary of the review of fractures (Appendix 11). For all fracture sites, the pooled estimates of the RR of fracture after etidronate were similar to those obtained using the definition of secondary prevention trials with the >20% baseline fracture rate.

c) Adverse events

A summary of the adverse drug events (ADEs) reported in the 11 randomized placebo-controlled trials of etidronate is provided in Appendix 12. The reported events were similar when etidronate was compared to placebo.

Toxicity and withdrawals

The number of discontinuations due to adverse events (AEs) or dropouts overall was available and analyzed for five[19,48,52,61,78] and 10[19,48,52,58,61,64,68,69,74,78] etidronate trials respectively. The pooled estimate demonstrated no significant difference between etidronate and placebo for the risk of withdrawal because of AEs [RR 0.61 (95% CI: 0.25; 1.49)], or for dropouts overall [RR 0.91 (95% CI: 0.71; 1.26)]. Results were consistent across the trials.

4.3 Results for Alendronate

4.3.1 Quantity of research available

The literature search revealed 708 citations (Figure 6). Of these, 77 articles were retrieved for further scrutiny.[79-155] A total of 66 articles were excluded for various reasons, including lack of appropriate control group,[86,87,95,102,106,118,121,124,128,135,136,139-141,145,147,148,150,154] lack of fracture outcome,[88,93,94,96,101,107,119,120,122,126,131,133,138,144,149,152,153,155] lack of appropriate fracture data (i.e., reported as AEs or unspecified),[80,82,90,92,104,112,117,127] lack of randomization,[114,143] extension or discontinuation studies,[91,111,132,134,142] duplicate report or earlier report of another

study,[79,83,85,103,115,146,151] and duration of therapy <1 year.[97,98,109,113,125,129,137] If duplicate reports of the same study were found in preliminary abstracts and articles, the data from the most complete data set were analyzed. Eleven trials met the selection criteria for inclusion in this report.[81,84,89,99,100,105,108,110,116,123,130]

4.3.2 Trial characteristics

The characteristics of the 11 selected trials are shown in Table 7. Of the total of 12,099 women who were enrolled, 5,525 received a placebo. Three trials were in primary prevention,[81,100,116] and the other eight involved women with low BMD on densitometry or high prevalence of vertebral fracture.[84,89,99,105,108,110,123,130] Three trials, including the largest secondary prevention trial — the Fracture Intervention Trial (FIT) — used an initial dose of 5 mg, and then switched to 10 mg for the final years.[84,100,110] We excluded data from the HRT arm of the Hosking *et al.* study.[116]

Three trials concealed allocation,[89,100,116] and for the remainder, it was unclear. Two trials[84,100] achieved a loss to follow-up of <5%; five trials[81,99,116,123,130] had losses to follow-up from 5% to 20%; three trials[89,105,110] had losses to follow-up >20%, and one trial[108] did not report losses to follow-up.

4.3.3 Data analysis and synthesis

a) Effect on fractures

Table 8 provides a summary of the review of fractures for the base case with the standard 10 mg dose of alendronate. The base case represents the longest treatment duration and use of the baseline denominators for the number of patients in the trial. The pooled estimate of the RR was significant for secondary prevention of vertebral, non-vertebral, hip, and wrist fractures. It was not significant for primary prevention, with the exception of vertebral fractures.

Vertebral fractures

Vertebral fractures were reported in eight of 11 trials. In two trials, no fractures occurred in either treatment group.[81,99] In the four trials[84,100,105,123] that could be analyzed, the pooled estimate of RR of vertebral fractures demonstrated a significant reduction (45%) in vertebral fractures [RR 0.55 (95% CI: 0.45; 0.67)] (Table 8 and Figure 7). This supports a fracture risk reduction with alendronate. Results were consistent across the four trials (p=0.61). There was a significant reduction in vertebral fracture for primary and secondary prevention trials. Estimates for the risk reduction were similar for the primary [RR 0.55 (95% CI: 0.38; 0.80)] and secondary [RR 0.55 (95% CI: 0.43; 0.69)] prevention trials.

Corresponding to the significant RRR of 45% for the primary or secondary prevention of vertebral fractures, the absolute measures ARR and NNT of the five-year risk of vertebral fracture after treatment with alendronate were calculated for different levels of increasing risk, as given by the FI (Appendix 13, and Appendix 14 for increasing age). For the illustrative case of the patient with an FI of six to seven, the ARR in vertebral fracture was 3.2% (i.e., a reduction in risk from 7.1% to 3.9%) and the NNT was 31 (i.e., 31 patients would need to be treated to avoid one vertebral fracture). Across the range of increasing FI risk, the ARR for vertebral fracture ranged from 0.5% to 5.0%, and the NNT to avoid one vertebral fracture ranged from 200 to 20. For the illustrative patient in the group who were 60 to 64 years old, the ARR for the first vertebral fracture was 0.5% (i.e., a reduction in risk from 1.0% to 0.55%) and the NNT was 222 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 4.4% (i.e., a reduction in risk from 9.7% to 5.3%) and the NNT was 23 patients treated to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first vertebral fracture increased from 0.1% for the youngest group (50 to 54 years old) to 2.1% in the oldest group

(90+ years). The NNT decreased from 1,111 to 47. For the subsequent fracture, ARR increased from 0.2% to 12.6%, and the NNT decreased from 444 to eight.

Non-vertebral fractures

Non-vertebral fractures were reported in seven trials examining a daily alendronate dose of 10 mg. One trial did not report fractures by treatment group,[99] and one trial reported that no fractures occurred in either treatment group.[81] The pooled estimate of the RR of non-vertebral fractures from the five trials[84,100,110,123,130] that could be analyzed showed a significant reduction (16%) in non-vertebral fractures [RR 0.84 (95% CI: 0.74; 0.94)] (Table 8 and Figure 8). Results were consistent across the five trials (p=0.29). Although the primary and secondary prevention trials differed in significance of the reduction in risk of non-vertebral fractures, the non-significant reduction [RR 0.89 (95% CI: 0.76; 1.04)] in the one primary trial was not clearly different from the significant reduction [RR 0.77 (95% CI: 0.64, 0.92)] in the four secondary prevention trials.

Figure 6: Literature search for alendronate

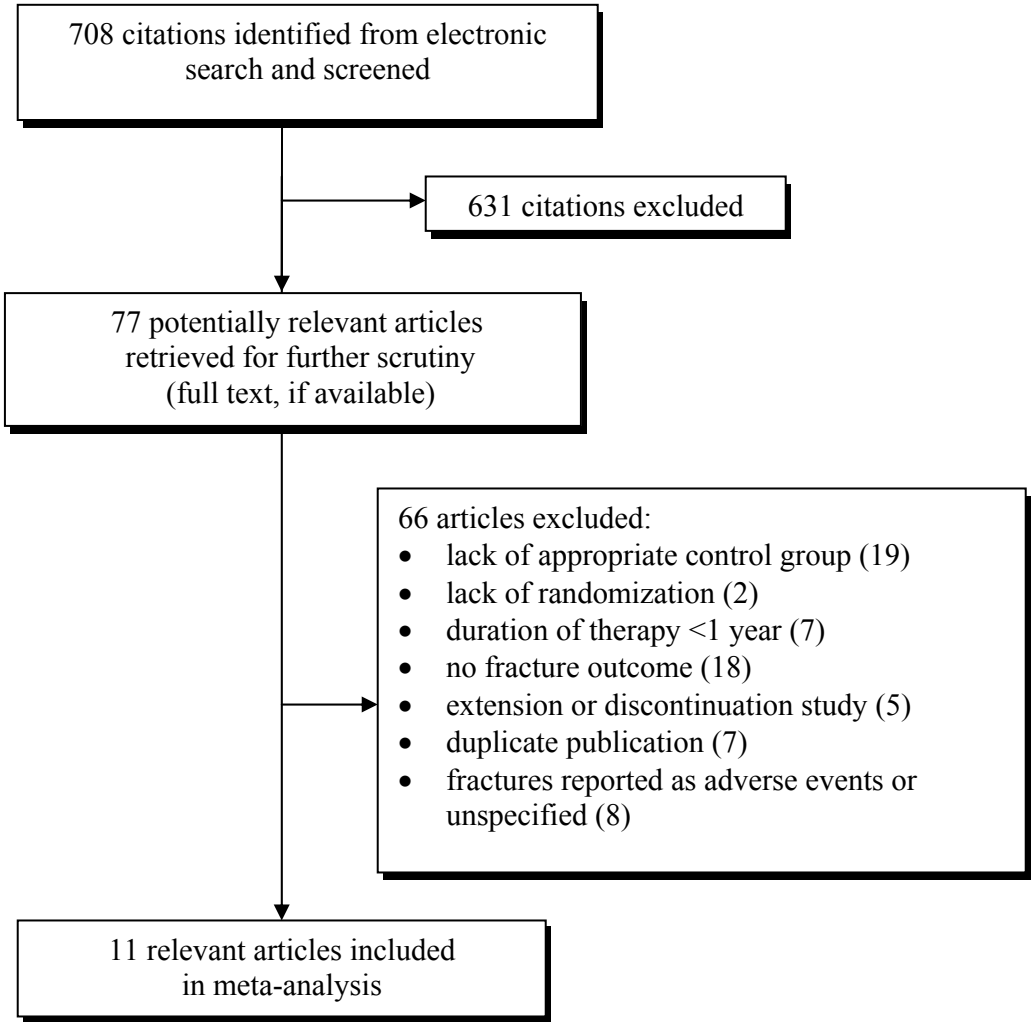


Figure 7: RR of vertebral fracture after alendronate (10 mg)

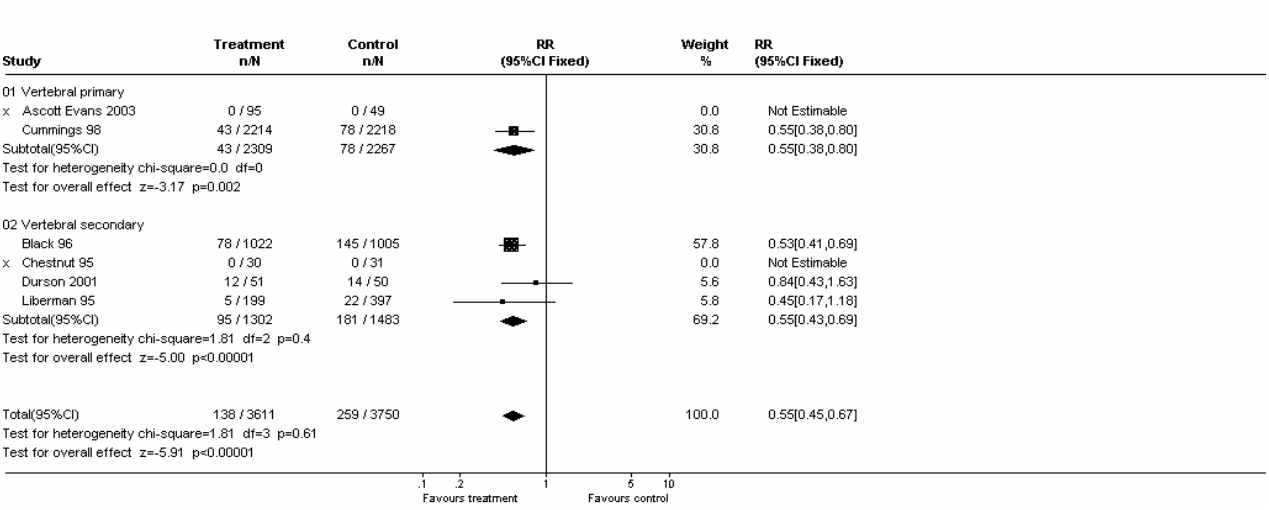


Figure 8: RR of non-vertebral fracture after alendronate (10 mg)

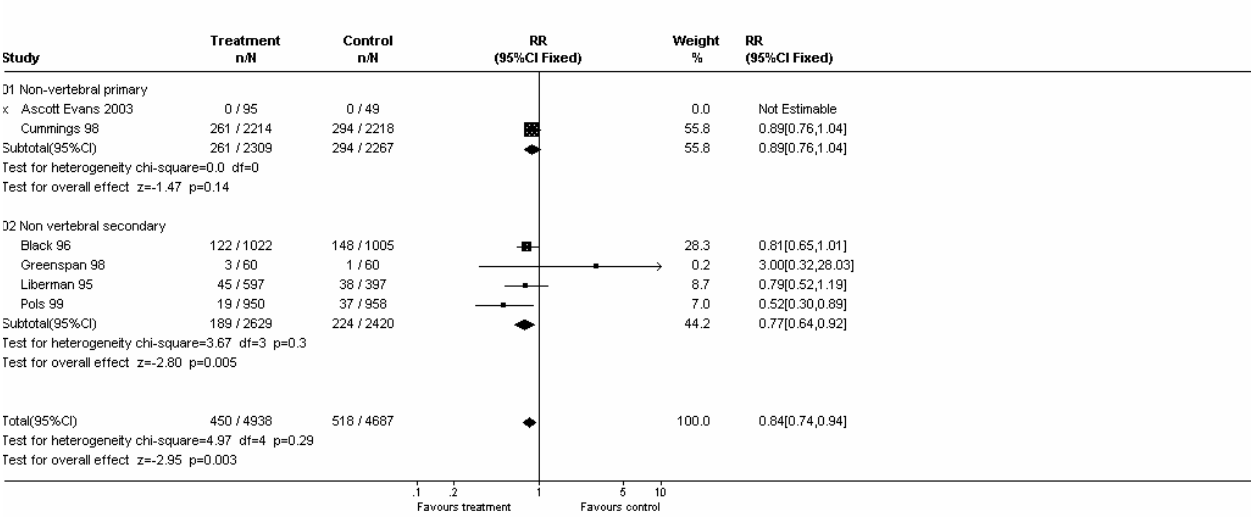


Table 7: Characteristics of included studies for alendronate						
Trial (primary or secondary prevention)*	**Number of Participants (treatments/ controls)**	**Mean Age (SD); Years Since Menopause (SD); Baseline Calcium Intake/day; Lumbar BMD g/cm^2; T-score;† Vertebral Fracture Prevalence**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Ascott-Evans (primary)	144 (95/49)	age: 67.3 (6.6); YSM: 11.5 (7.3); calcium: not reported; BMD: not reported; T-score: −2.27 (0.65); fractures: 0%	alendronate 10 mg x 1 year versus placebo (calcium 500 mg/day)	1	vertebral, non-vertebral, hip, wrist	alendronate: 12/95 (12.6%); placebo: 13/49 (26.5%); total: 25/144 (17.4%)
Black (secondary)	2,027 (1,022/1,005)	age: 71.0 (5.6); YSM: not reported; calcium: 636 (407) mg/day; BMD (hip): 0.57 g/cm ^{2} (0.07); T-score (hip): −3.3; fractures : 100%	alendronate 5 mg x 2 years, then 10 mg x 1 year versus placebo (if intake <1,000 mg, then received 500 mg Ca and 250 IU vitamin D)	3	vertebral (radiographic), vertebral (clinical), non-vertebral, hip, wrist	alendronate (available radiographs): 44 (4.2%); placebo (available radiographs): 37/1,005 (3.7%) ; total (available radiographs): 81/2,027 (4.0%) ; total (lost to follow-up at close-out): 78/2,027 (3.8%)
Bone (secondary)	359 (86/89/93/91)	age: 70.4 (5.6); YSM: 24.2 (9.9); calcium: 891(629) mg/day; BMD: 0.71 g/cm^2 (0.08); T-score: −3.1; fractures: 37.4%	alendronate 1 mg, or 2.5 mg; or 5 mg versus placebo (500 mg calcium/day)	2	vertebral; non-vertebral	total (for BMD analysis): 131/359 (36.5%)

Table 7: Characteristics of included studies for alendronate						
Trial (primary or secondary prevention)*	**Number of Participants (treatments/ controls)**	**Mean Age (SD); Years Since Menopause (SD); Baseline Calcium Intake/day; Lumbar BMD g/cm^2; T-score;† Vertebral Fracture Prevalence**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Chesnut (secondary)	188 (32/30/32/32/31)	age: 63.04 (6.27); YSM: 15.6 (7.3); calcium: 853 (516) mg/day; BMD: 0.75 g/cm^2 (0.09); T-score: −2.7; fractures : 0%	alendronate 5 mg/day or 10 mg/day for 2 years; 20 mg/day or 40 mg/day for 1 year, followed by 1 year of placebo; or 40 mg for 3 months, followed by 2.5 mg for 21 months versus placebo for 2 years (500 mg calcium/day)	2	vertebral, non-vertebral (not included in analysis as not reported by study group)	total: 34/188 (18%)
Cummings (primary)	4,432 (2,214/2,218)	age : 67.6 (6.1); YSM: not reported; calcium: 636 (400) mg/day; BMD: 0.84 g/cm^2 (0.13); T-score: −1.9, fractures : 0%	alendronate 5 mg for 2 years, then increased to 10 mg for 2 years versus placebo (if intake <1,000 mg, then received 500 mg Ca and 250 IU vitamin D)	4	vertebral, non-vertebral, hip, wrist	total (lost to follow-up at close-out) 160/4,432 (3.6%)
Dursun (secondary)	101 (51/50)	age: 61 (7.8); YSM: 15.59 (8.04); calcium: not reported; BMD: 0.84 g/cm (0.08); T-score: −1.9; fractures : not reported	alendronate 10mg/day plus calcium 1,000 mg/day x 1 year versus calcium 1,000 mg	1	vertebral	alendronate: 13/51 (25.5%); control: 15/50 (30.0%); total: 28/101 (28%)

Table 7: Characteristics of included studies for alendronate						
Trial (primary or secondary prevention)*	**Number of Participants (treatments/ controls)**	**Mean Age (SD); Years Since Menopause (SD); Baseline Calcium Intake/day; Lumbar BMD g/cm^2; T-score;† Vertebral Fracture Prevalence**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Greenspan (secondary)	120 (60/60)	age: 70 (4.6); YSM: not reported; calcium: 719 (465) mg/day; BMD: 0.57 g/cm^2 (0.11) ; T-score: −4.3; fractures: not reported	alendronate 5 mg x 1.5 year, then increased to 10 mg x 1 year versus placebo, (if Ca intake <1,000 mg, then received 250 mg Ca or 125 IU vitamin D/day)	2.5	non-vertebral, hip, wrist	alendronate: 14/60 (23.3%); placebo: 15/60 (25.0%); total: 29/120 (24.2%)
Greenspan (secondary)	327 (163/164)	age: 78.5 (range 65 to 91); YSM: not reported; calcium: not reported; BMD: not reported; T-score: (mean range hip and spine) −3.5 to −2.4; fractures: (history of any) 55%	alendronate 10 mg/day x 2 years versus placebo (vitamin D 400 IU/day and if dietary calcium was <500 mg/day, they received calcium 500 mg/day)	2	hip	not reported
Hosking (primary)	1,499 (499/498/502) (HRT group not included)	age: 53 (4); YSM: 6 (5); calcium: 923 (505) mg/day; BMD: 0.94 g/cm^2 (0.12); T-score: −1.0, fractures: <10%	alendronate 2.5 or 5 mg versus placebo (<500 mg calcium intake, encouraged to increase)	2	vertebral, non-vertebral	alendronate: 2.5 mg 92/499 (18.4%); alendronate 5 mg: 102/498 (20.5%); placebo: 93/502 (18.5%); total: 287/1,499 (19.1%)

Table 7: Characteristics of included studies for alendronate						
Trial (primary or secondary prevention)*	**Number of Participants (treatments/ controls)**	**Mean Age (SD); Years Since Menopause (SD); Baseline Calcium Intake/day; Lumbar BMD g/cm^2; T-score;† Vertebral Fracture Prevalence**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Liberman (secondary)	994 (597/397)	age:64 (7); YSM: 16.5; calcium: 739 (537) mg/day; BMD: 0.71; T-score: −3.1, fractures: 21%	alendronate 5 mg, 10 mg, or 20 mg versus placebo (500 mg calcium/day)	3	vertebral, non-vertebral, hip, wrist	alendronate: 97/597 (16.2%); placebo: 65/397 (16.5%); total: 162/994 (16.3 %)
Pols (secondary)	1,908 (950/958)	age: 62.8 (7.4); YSM: 15.9 (1.5); calcium: NA; BMD: 0.72 g/cm^2 (0.08); T-score: −2.97; fractures: not reported	alendronate 10 mg versus placebo (500 mg calcium/day)	1	non-vertebral, hip, wrist	alendronate: 118/950 (12.4%); control: 93/958 (9.7%); total: 211/1,908 (11.1 %)

*Refers to a priori definition of primary and secondary prevention; †t-score calculated using lumbar spine BMD [(LS BMD−1.047)/0.110]; YSM=years since menopause; BMD=bone mineral density; NA=not available.

Table 8: Weighted RR of fracture after alendronate (10 mg)						
Fracture Sites	**Primary or Secondary Prevention**	**Number of Trials**	**Number of Participants (treatment/ control)**	**RR (95% CI)**	**Association p value**	**Heterogeneity p value**
vertebral	overall	4	3,486/3,670	0.55 (0.45; 0.67)	<0.0001	0.61
	primary	1	2,214/2,218	0.55 (0.38; 0.80)	0.002	N/A
	secondary	3	1,272/1,452	0.55 (0.43; 0.69)	<0.0001	0.4
non-vertebral	overall	5	4,843/4,638	0.84 (0.74; 0.94)	0.003	0.29
	primary	1	2,214/2,218	0.89 (0.76; 1.04)	0.14	N/A
	secondary	4	2,629/2,420	0.77 (0.64; 0.92)	0.005	0.3
hip	overall	6	5,005/4,802	0.61 (0.40; 0.92)	0.02	0.84
	primary	1	2,214/2,218	0.79 (0.44; 1.44)	0.4	N/A
	secondary	5	2,792/2,584	0.47 (0.26; 0.85)	0.01	0.96
wrist	overall	5	4,843/4,742	0.68 (0.34; 1.37)*	0.3	0.0007
	primary	1	2,214/2,218	1.19 (0.87; 1.62)	0.3	N/A
	secondary	4	2,629/2,524	0.52 (0.25; 1.08)*	0.08	0.069

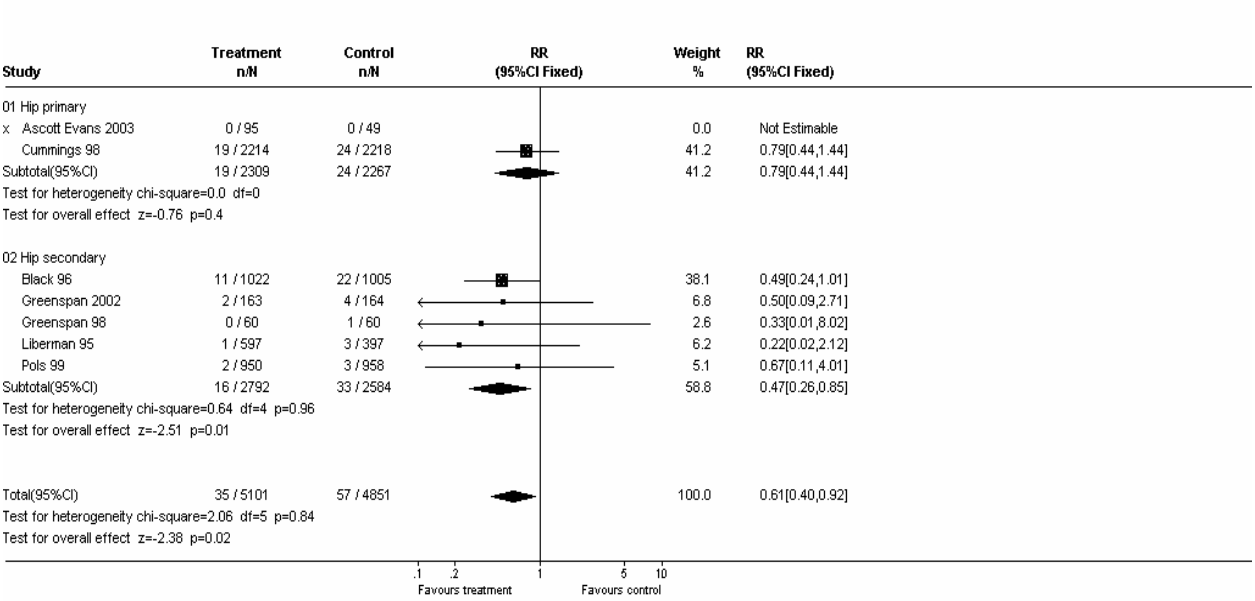
*RR estimate based on random effects model; RR=relative risk; CI=confidence interval; N/A=not applicable.

Corresponding to the significant RRR of 23% for the secondary prevention of non-vertebral fractures, the absolute measures ARR and NNT of the five-year risk of non-vertebral fracture after treatment with alendronate were calculated for different levels of increasing risk as measured by the FI (Appendix 13), and for increasing age (Appendix 14). For the illustrative case of the patient with a FI of six to seven, the ARR in non-vertebral fracture was 4.6% (i.e., a reduction in risk from 19.8% to 15.2%) and the NNT was 22 (i.e., 22 patients need to be treated to avoid one non-vertebral fracture). Across the range of increasing FI risk, ARR for non-vertebral fracture ranged from 2.0% to 6.3%, and NNT to avoid one non-vertebral fracture ranged from 50 to 16. For the illustrative patient in the group who were 60 to 64 years old, the ARR for the first non-vertebral fracture was 0.7% (i.e., a reduction in risk from 3.1% to 2.4%). The NNT was 140 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 1.4% (i.e., a reduction in risk from 6.2% to 4.8%). The NNT was 70 patients treated to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first non-vertebral fracture increased from 0.4% for the youngest group (50 to 54 years old) to 8.1% in the oldest group (90+ years). The NNT decreased from 272 to 12. The ARR for subsequent fracture increased from 0.6% to 8.7% and the NNT decreased from 167 to 12.

Hip fractures

Hip fractures were reported in seven trials,[81,84,100,108,110,123,130] with one trial reporting that no fractures occurred in either treatment group.[81] The pooled estimate of the RR of hip fractures from the six trials resulted in a significant reduction (39%) in hip fractures [RR 0.61 (95% CI: 0.40; 0.92)] (Table 8 and Figure 9). The results were consistent across the six trials (p=0.84). The reduction in the risk of hip fractures for the one primary prevention trial was insignificant [RR 0.79 (95% CI: 0.44; 1.44)] compared to the significant reduction demonstrated by the five secondary prevention trials [RR 0.47 (95% CI: 0.26; 0.85)].

Figure 9: RR of hip fracture after alendronate (10 mg)

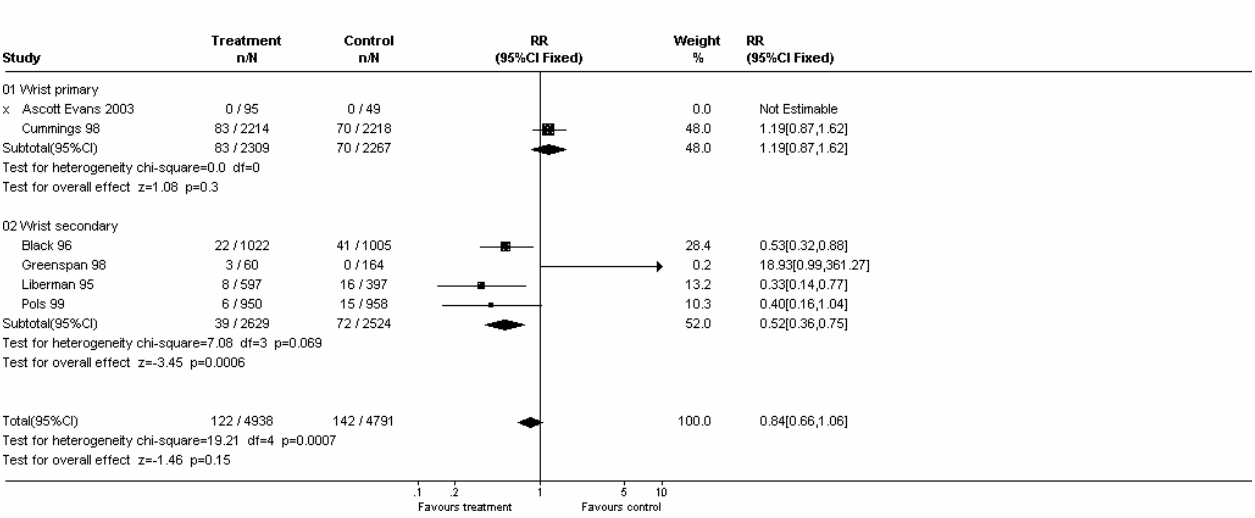


Corresponding to the significant RRR of 53% for the secondary prevention of hip fractures, the absolute measures ARR and NNT for the five-year risk of hip fracture after treatment with alendronate were calculated for different levels of increasing risk, as measured by the FI (Appendix 13) and for increasing age (Appendix 14). For the illustrative case of the patient with an FI of six to seven, the ARR in hip fracture was 2.1% (i.e., a reduction in risk from 3.9% to 1.8%), and the NNT was 48 (i.e., 48 patients need to be treated to avoid one hip fracture). Across the range of increasing FI risk, the ARR for hip fracture ranged from 0.2% to 4.6%. The NNT to avoid one hip fracture ranged from 500 to 22. For the illustrative patient in the group who were 60 to 64 years old, the ARR for the first hip fracture was 0.1% (i.e., a reduction in risk from 0.2% to 0.1%). The NNT was 943 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 0.1% (i.e., a reduction in risk from 0.2% to 0.1%). The NNT was 943 patients treated to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first hip fracture increased from <0.05% for the youngest group (50 to 54 years old) to 11.1% in the oldest group (90+ years). The NNT decreased from 272 to nine. For the subsequent fracture, the ARR increased from <0.05% to 12.1%, and the NNT decreased from 472 to eight.

Wrist fractures

Wrist fractures were reported in six trials,[81,84,100,110,123,130] and one trial reported that no fractures occurred in either treatment group.[81] Results were inconsistent across the five trials that reported wrist fractures (p=0.0007) (Figure 10). The pooled estimate of the RR of wrist fracture from these five trials resulted in a non-significant reduction in fractures, using the random effects [RR 0.68 (95% CI: 0.34; 1.37)] (Table 8) or the fixed effect approach [(RR 0.84, 95%CI: 0.66, 1.06)], (Figure 10). We could not identify a statistically significant effect of alendronate when used for the primary prevention of wrist fractures (RR 1.19, 95% CI: 0.87; 1.62) (Table 8 and Figure 10). In the four secondary prevention trials, data analysis is more complex. When the fixed effect is used, a statistically significant effect is observed (RR 0.52, 95% CI: 0.36; 0.75). However, such an approach is associated with statistical heterogeneity (p=0,069), mainly due to the Greenspan *et al.* trial[110] (weight=0.2% of all studies) (Figure 10). When a random effects approach is used, the pooled RR reported becomes non-significant (RR 0.52, 95% CI: 0.25; 1.08).

Figure 10: RR of wrist fracture after alendronate (10 mg)



b) Additional analysis

Person-years

Results were similar for vertebral, non-vertebral, hip, and wrist fractures when person-years were used (Table 9). The pooled estimates of the RR for the secondary prevention trials all showed a significant risk reduction of fracture for all sites. Because of the lack of consistency among the trials, a random effects estimate was used for the pooled estimate for vertebral fractures.There was no inconsistency among the secondary prevention trials for wrist fractures. The risk estimates obtained from the one primary prevention trial for vertebral fracture remained significant, although results were non-significant for the other fracture sites.

Subgroup analysis

Treatment duration: There were no trends over years of treatments that deviated from the overall RR estimates (Appendix 15), with the possible exception of increased risk of hip fracture in later years.

Treatment dose: For the 5 mg dose of alendronate, fracture data were only available for the vertebral and non-vertebral sites for secondary prevention trials (Appendices 16, 17, and 18). For vertebral fractures, the decrease in risk of fracture was statistically significant; there was a further decrease in risk with the 5 mg compared to the 10 mg dose. The decrease in risk for non-vertebral fractures was not statistically significant, and was larger for the 5 mg compared to the 10 mg dose.

Sensitivity analysis

Baseline versus follow-up denominators: We prepared a summary of the review of fractures in Appendix 19 by using the data available for longest treatment duration, standard dose of alendronate (10 mg), and follow-up denominators for the number of patients in the trials. These data are also provided by years of treatment in Appendix 20. The pooled estimates of the RR of fracture after alendronate were similar to those obtained using the baseline denominators.

Random versus fixed effects model: There were instances where heterogeneity of the trial results required a random effects model. In general, results obtained using the random and fixed effects models were similar. One exception was the wrist fracture results for secondary prevention trials when the Greenspan *et al*. trial[110] was included, because the fixed effect result was significant in comparison to the random effects result.

Baseline vertebral fracture rate

A summary of the review of fractures was prepared using baseline vertebral fracture rates (i.e., 100%, >80%, >60%, >40%, >20%) for defining secondary prevention trials (Appendix 21). For vertebral fractures, the pooled estimates of the RR of fracture after alendronate were similar to those obtained using the definition of secondary prevention trials with the >20% baseline fracture rate. Although the result for non-vertebral and hip fractures became non-significant when the criteria increased from >20% to >40% and >40% to >60% respectively, the relative risk of fracture was the same. The confidence intervals were now wider with the exclusion of the study by Liberman *et al.*[123] for non-vertebral fractures and Greenspan *et al.*[108] for hip fractures. For wrist fractures, the non-significant result became significant when the >20% baseline fracture rate was used without the BMD and age criteria, because a fixed effects model could be used.

c) Adverse events

A summary of the ADEs reported in the 11 randomized placebo-controlled trials of alendronate is provided in Appendix 22. In general, the reported events were similar between alendronate and placebo.

Table 9: Weighted RR of fracture after alendronate (10 mg) in person-years

Fracture Sites	Primary or Secondary Prevention	Number of Trials	Number of Participants (treatment/ control) Person-Years	RR (95% CI)	Association p value	Heterogeneity p value
vertebral	overall	4	12,047/12,800	0.49 (0.35;0.68)*	<0.0001	0.097
	primary	1	8,639/8,723	0.53 (0.37; 0.76)	0.0005	N/A
	secondary	3	3,408/4,077	0.49 (0.29; 0.82)*	0.007	0.084
non-vertebral	overall	5	14,270/13,952	0.83 (0.74; 0.94)	0.004	0.17
	primary	1	8,658/8,872	0.91 (0.77; 1.07)	0.3	N/A
	secondary	4	5,612/5,080	0.74 (0.61; 0.89)	0.002	0.27
hip	overall	6	15,121/14,605	0.61 (0.40; 0.92)	0.02	0.84
	primary	1	9,299/9,316	0.79 (0.43; 1.45)	0.4	N/A
	secondary	5	5,822/5,289	0.47 (0.26; 0.85)	0.01	0.96
wrist	overall	5	14,795/14,277	0.65 (0.34; 1.25)*	0.19	0.0024
	primary	1	9,299/9,316	1.19 (0.87; 1.63)	0.3	N/A
	secondary	4	5,496/4,961	0.50 (0.34; 0.73)	0.0004	0.25

*RR estimate based on random effects model; RR=relative risk; CI=confidence interval; N/A=not applicable.

Toxicity and withdrawals

Discontinuations because of AEs or dropouts were available and analyzed for six[81,84,89,100,105,130] and five[81,105,110,116,130] alendronate trials respectively. The pooled estimate demonstrated no statistical difference between alendronate and placebo for the risk of discontinuing medication due to AEs [RR 0.95 (95% CI: 0.83; 1.09)] or for dropouts overall [RR 1.10 (95% CI: 0.94; 1.29)]. Results were consistent across the trials.

4.4 Results for Risedronate

4.4.1 Quantity of research available

The literature search revealed 121 citations (Figure 11). Of these, 29 articles were retrieved for further scrutiny.[117,156-183] A total of 23 articles were excluded for various reasons, including lack of appropriate control group,[156,163,165,167] lack of fracture outcome,[158,160,166] lack of appropriate fracture data (i.e., reported as AEs and unspecified),[117] lack of randomization,[162,168,175,178,180] extension or discontinuation study,[179] duplicate report or earlier report of another study,[159,171,174,176,177,181,182] duration of therapy <1 year,[183] and no extractable data.[169] If duplicate reports of the same study were found in preliminary abstracts and articles, the data from the most complete data set were analyzed. Six trials met the selection criteria.[157,161,164,170,172,173]

4.4.2 Trial characteristics

The characteristics of the six selected trials are shown in Table 10. Of the 13,795 women enrolled in these trials; 4,621 received a placebo. One trial was a primary prevention trial,[172] and the other five involved women with low BMD on densitometry or who had experienced previous fractures.[157,161,164,170,173] All trials had three treatment arms that included two involving risedronate at different doses (i.e., 2.5 mg or 5 mg) or different schedules, and a placebo arm. To avoid duplication of data in the pooled estimates, we did not include data from both risedronate arms in any single meta-analysis.

Treatment allocation was concealed in one trial,[164] and was unclear for the other five trials. All six trials had losses to follow-up that were >20%. As examples, one trial[161] had losses to follow-up of between 20% and 30%, three trials[157,164,170] had losses between 30% and 40%, and two trials[172,173] exceeded 40%.

4.4.3 Data analysis and synthesis

a) Effect on fractures

The trial by Mortensen *et al.*[172] was the only primary prevention trial for risedronate included in the review. It reported no fractures. As a result, risk estimates for primary prevention could not be estimated, and only risks from secondary prevention trials were reported. A summary of the review of fractures with the standard dose of risedronate (5 mg) for the base case is shown in Table 11 (i.e., the longest treatment duration in the trial, and using the baseline denominators for the number of patients). In general, for each of vertebral, non-vertebral, and hip fracture, the pooled estimate of the RR of fracture was significant for secondary prevention, with the exception of wrist fracture, which was not significant.

Vertebral fractures

Vertebral fractures were reported in four secondary prevention trials.[157,161,164,173] One study was excluded from analysis, because of the apparent inclusion of an off-drug treatment period in the data.[157] The pooled estimate of the RR of vertebral fractures from the three trials[161,164,173] that could be analyzed showed a significant reduction (39%) in vertebral fractures [RR 0.61 (95% CI: 0.50, 0.76)] (Figure 12). This demonstrates a fracture risk reduction with risedronate 5 mg daily. Results are consistent across studies (p=0.75).

Corresponding to the significant RRR of 39% for the secondary prevention of vertebral fractures, the absolute measures ARR and NNT of the five-year risk of vertebral fracture after treatment with risedronate were calculated for different levels of increasing risk, as given by the FI. Results are provided in Appendix 23 and in Appendix 24 for increasing age. For the illustrative case of the patient with an FI of six to seven, the ARR in vertebral fracture was 2.8 (i.e., a reduction in risk from 7.1% to 4.3%), and the NNT was 36 (i.e., 36 patients need to be treated to avoid one vertebral fracture).

Figure 11: Literature search for risedronate

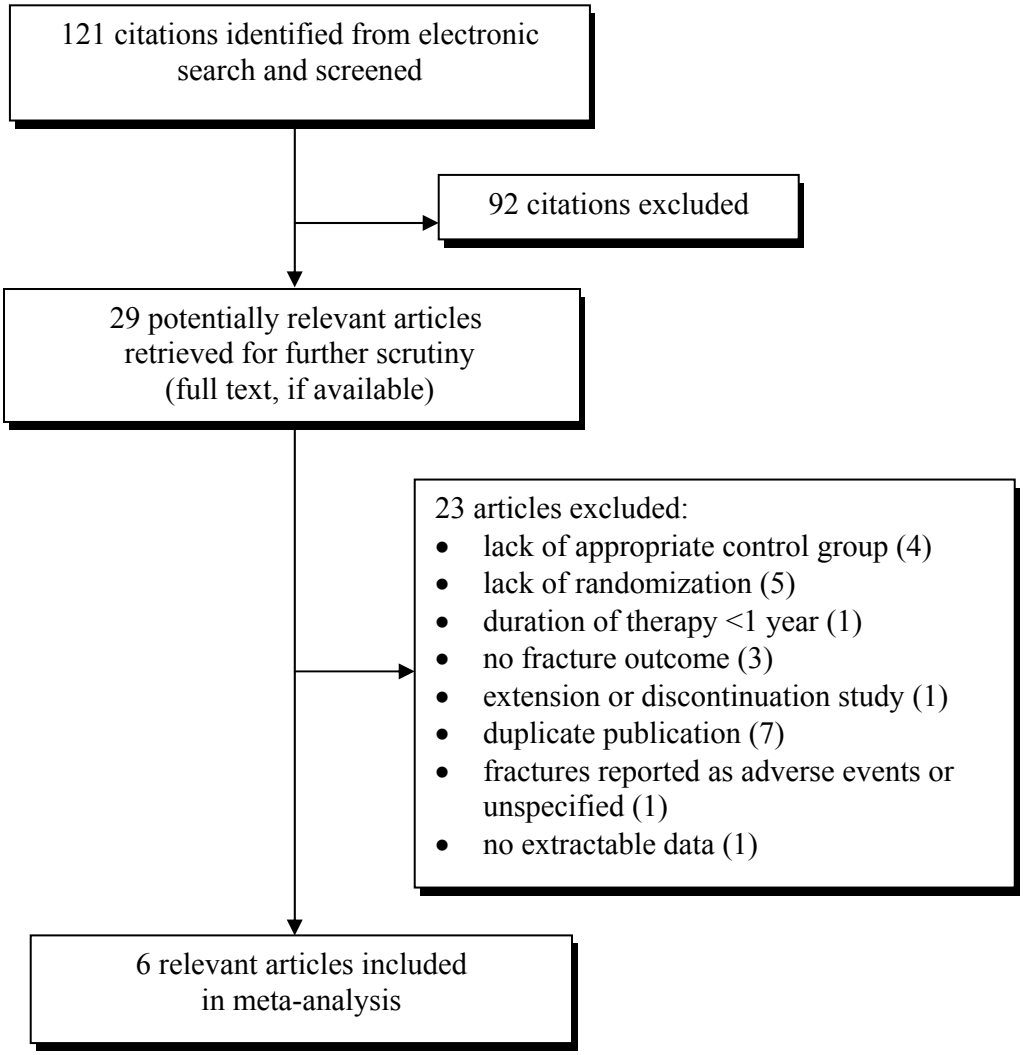


Table 10: Characteristics of included studies for risedronate						
Trial (primary or secondary prevention)*	**Number of Patients (treatments/ control)**	**Mean age (SD); Years Since Menopause (SD); Baseline Calcium Intake; Lumbar BMD g/cm^2; T-score ;† Prevalent Vertebral Fractures**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
Clemmesen (secondary)	132 (44/44/44)	age: 68.3 (5.7); YSM: 20.3 (7.3); calcium: not reported; BMD: 0.78 (0.14) g/cm^2; T-score: −2.4; fractures: 100%	risedronate 2.5 mg/day or cyclical risedronate 2.5 mg/day for 2 weeks, followed by placebo for 10 weeks versus placebo (calcium 1,000 mg/day)	2 on drug plus 3rd year drug free follow-up	vertebral, non-vertebral, (study not included in analysis as data appeared to include off-drug treatment period)	continuous: 15/44 (34.1%); cyclic: 11/44 (25.0%); placebo: 13/44 (29.5%); total: 39/132 (29.5%)
Fogelman (secondary)	543 (184/177/180)	age: 64.7 (7.2); YSM: 17.7 (9.4); calcium: not reported; BMD: 0.74 (0.08); T-score: −2.9; fractures: 30%	risedronate 2.5 mg/day or risedronate 5 mg/day versus placebo (calcium 1,000 mg/day)	2 (2.5 mg patients from 9 of 13 centres (N=76) discontinued before end of study because of protocol amendment)	vertebral, non-vertebral	2.5 mg: 111/184 (60.0%); 5.0 mg: 38/177 (21.5%); placebo: 37/180 (20.6%); total: 186/543 (34.3%); [not including protocol amendment: 110/467 (23.6%)]
Harris (secondary)	2,458 (817/821/820)	age: 69 (7.3); YSM: 24 (9.9); calcium: not reported; BMD: 0.83 g/cm^2 (0.16); T-score: −2.4 fractures: 81%	risedronate 2.5 mg/day or risedronate 5 mg/day versus placebo (calcium 1,000 mg/day and if 25-	3 (2.5 mg/day dose discontinued at 1 year because of protocol amendment)	vertebral, non-vertebral, hip, wrist	2.5 mg: 238/817 (29.1%); 5.0 mg: 332/821 (40.4%); placebo: 370/820 (45.1%); total: 940/2458 (38.2%)

Table 10: Characteristics of included studies for risedronate						
Trial (primary or secondary prevention)*	**Number of Patients (treatments/ control)**	**Mean age (SD); Years Since Menopause (SD); Baseline Calcium Intake; Lumbar BMD g/cm^2; T-score ;† Prevalent Vertebral Fractures**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
			hydroxyvitamin D level <40 nmol/L, they received ≤500 IU/day cholecalciferol			
McClung (secondary)	9,331 (3093/3104/3134)	age: 78.0 (9.7); YSM: 31.8 (19.3); calcium: not reported; BMD: not reported; T-score (femoral): −3.7; fractures: 42%	risedronate 2.5 mg/day or risedronate 5 mg/day versus placebo (calcium 1,000 mg/day and if 25-hydroxyvitamin level <40 nmol/L, they received vitamin D 500 IU/day)	3	non-vertebral, hip	2.5/ 5.0 mg combined: 2,197/6,197 (35.5%); placebo: 1,127/3,134 (35.9%); total: 3,324/9,331 (35.6%)
Mortensen (primary)	111 (37/38/36)	age: 51.2 (3.8); YSM: 2.7 (1.7); calcium: 977 (535) mg/d; BMD: 0.94 (0.11) g/cm^2; T-score: −1.0; fractures: 0% (excluded)	risedronate 5 mg/day or cyclical risedronate 5 mg/day for 1st 2 weeks of every calendar month, followed by placebo for remainder versus	2 years on drug plus 3rd year drug-free follow-up (patients given option to continue in study after completing 1st year)	vertebral, non-vertebral (data for non-vertebral not included in analysis, as data appeared to include off-drug treatment period),	continuous: 20/37 (54.1%); cyclic: 14/38 (36.8%); placebo: 15/36 (41.7%); total: 49/111 (44%)

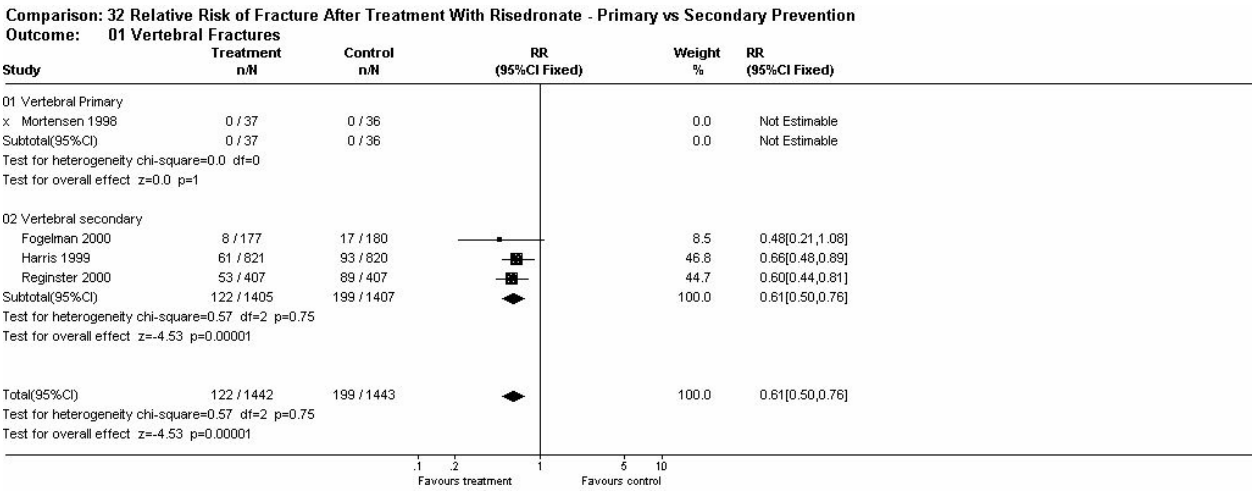
Table 10: Characteristics of included studies for risedronate						
Trial (primary or secondary prevention)*	**Number of Patients (treatments/ control)**	**Mean age (SD); Years Since Menopause (SD); Baseline Calcium Intake; Lumbar BMD g/cm^2; T-score ;† Prevalent Vertebral Fractures**	**Intervention (concurrent calcium or vitamin D supplements)**	**Duration (years)**	**Fracture Outcomes**	**Withdrawals (%)**
			placebo (not required to take supplemental calcium)		hip, wrist	
Reginster (secondary)	1,222 (408/407/407)	age: 71.0 (7.0); YSM: 24.4 (8.5); calcium: not reported; BMD: 0.79 g/cm^2 (0.15); T-score: −2.7; fractures: 100%	risedronate 2.5 mg/day or risedronate 5 mg/day versus placebo (calcium 1,000 mg/day and if 25-hydroxyvitamin level <40 nmol/L, they received vitamin D 500 IU/day)	3 (2.5 mg/dose discontinued at 2 years because of protocol amendment)	vertebral, non-vertebral, hip, wrist	2.5 mg (at 1year): 76/408 (18.6%); 5.0 mg (at 3 years): 156/407 (38.3%); placebo (at 3 years): 186/407 (45.7%); total for 5.0 mg and placebo: 342/814 (40%)

*Refers to a priori definition of treatment and prevention; †t-score calculated using lumbar spine BMD [(LS BMD −1.047)/0.110]; YSM=years since menopause; BMD=bone mineral density.

Table 11: Weighted RR of fracture after risedronate (5 mg)						
Fracture Sites	**Primary or Secondary Prevention**	**Number of Trials**	**Number of Participants (treatment/ control)**	**RR (95% CI)**	**Association p value**	**Heterogeneity p value**
vertebral	Overall	3	1,405/1,407	0.61 (0.50; 0.76)	<0.0001	0.75
	Primary	1	37/36	N/E	N/E	N/E
	secondary	3	1,405/1,407	0.61 (0.50; 0.76)	<0.0001	0.75
non-vertebral	Overall	4	7,602/4,541	0.80 (0.72; 0.90)	0.0002	0.43
	Primary	0	N/A	N/A	N/A	N/A
	secondary	4	7,602/4,541	0.80 (0.72; 0.90)	0.0002	0.43
hip	Overall	3	7,425/4,361	0.74 (0.59; 0.94)	0.01	0.95
	Primary	1	37/36	N/E	N/E	N/E
	secondary	3	7,425/4,361	0.74 (0.59; 0.94)	0.01	0.95
wrist	Overall	2	1,265/1,263	0.67 (0.42; 1.07)	0.10	0.81
	Primary	1	37/36	N/E	N/E	N/E
	secondary	2	1,228/1,227	0.67 (0.42; 1.07)	0.10	0.81

RR=relative risk; CI=confidence interval; N/E=not estimable; N/A=not applicable

Figure 12: RR of vertebral fracture after risedronate (5 mg)



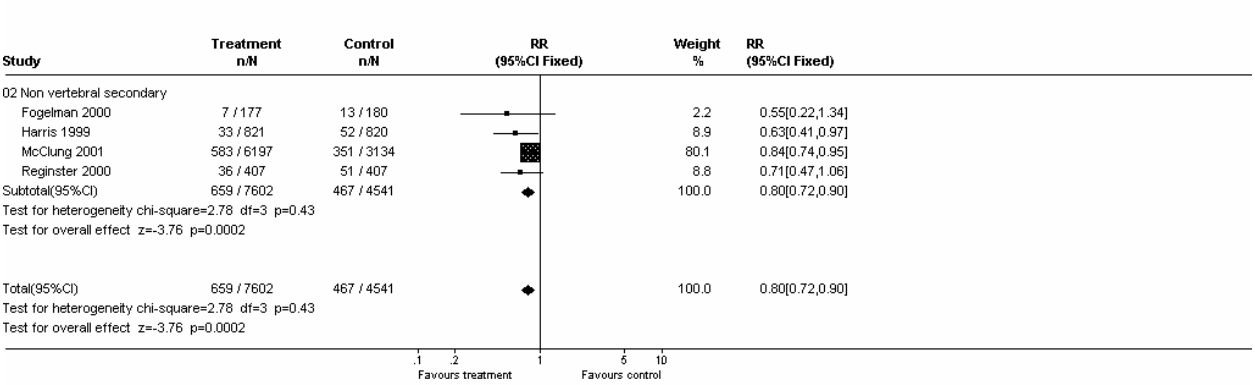
Across the range of increasing FI risk, the ARR for vertebral fracture ranged from 0.5% to 4.4%, and the NNT to avoid one vertebral fracture ranged from 214 to 23. For the illustrative patient in the age group 60 to 64 years, the ARR for the first vertebral fracture was 0.4% (i.e., a reduction in risk from 1.0% to 0.6%) and the NNT was 256 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 3.8% (i.e., a reduction in risk from 9.7% to 5.9%), and the NNT was 26 patients treated to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first vertebral fracture increased from 0.1% for the youngest group (50 to 54 years old) to 1.8% in the oldest group (90+ years), and the NNT decreased from 1,282 to 55. For the subsequent fracture, ARR increased from 0.2% to 10.9%, and the NNT decreased from 513 to nine.

Non-vertebral fractures

Non-vertebral fractures were reported in five secondary prevention trials.[157,161,164,170,173] The study[157] with a possible off-drug treatment period was excluded. The pooled estimate of the RR of non-vertebral fractures from the remaining four trials[161,164,170,173] demonstrated a significant 20% reduction in non-vertebral fractures [RR 0.80 (95% CI: 0.72; 0.90)]. Results (Figure 13) are consistent across studies (p=0.43).

Corresponding to the significant RRR of 20% for the secondary prevention of non-vertebral fractures, the absolute measures ARR and NNT of the five-year risk of non-vertebral fracture after treatment with risedronate were calculated for different levels of increasing risk, as given by the FI (Appendix 23) and for increasing age (Appendix 24). For the illustrative case of the patient with an FI of six to seven, the ARR in non-vertebral fracture was 4.0% (i.e., a reduction in risk from 19.8% to 15.8%) and the NNT was 25 (i.e., 25 patients need to be treated to avoid one non-vertebral fracture). Across the range of increasing FI risk, the ARR for non-vertebral fracture ranged from 1.7% to 5.5%, and the NNT to avoid one non-vertebral fracture ranged from 58 to 18.

Figure 13: RR of non-vertebral fracture after risedronate (5 mg)



For the illustrative patient in the age group 60 to 64 years, the ARR for the first non-vertebral fracture was 0.6% (i.e., a reduction in risk from 3.1% to 2.5%) and the NNT was 161 patients, to avoid the first fracture. The ARR for a subsequent fracture was 1.2% (i.e., a reduction in risk from 6.2% to 5.0%) and the NNT was 81 patients, to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first non-vertebral fracture increased from 0.3% for the youngest group (50 to 54 years old) to 7.0% in the oldest group (90+ years). The NNT decreased from 313 to 14. For the subsequent fracture, ARR increased from 0.5% to 7.5%, and NNT decreased from 192 to 13.

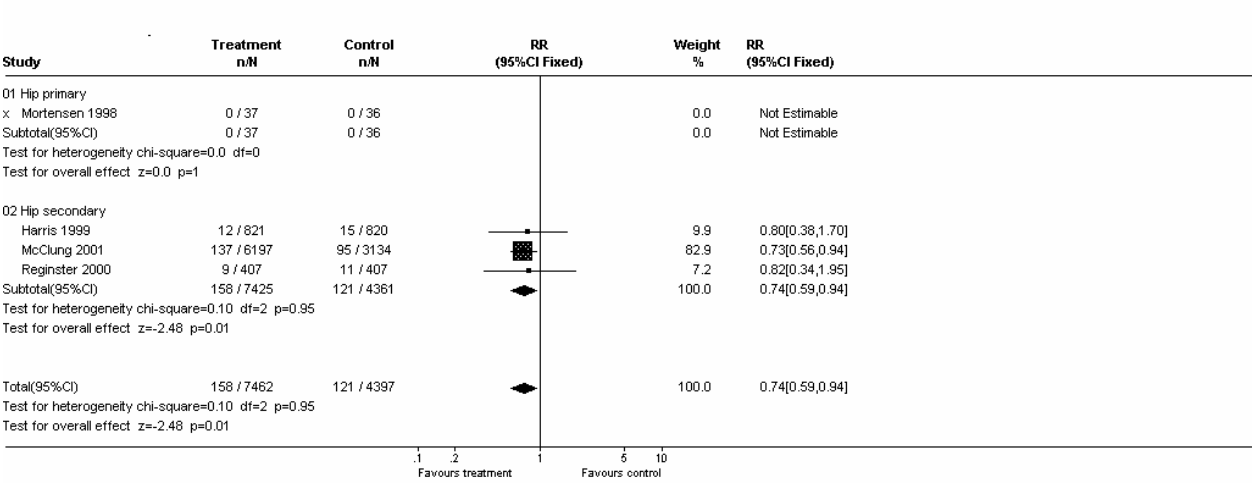
Hip fractures

Hip fractures were reported in three secondary prevention trials.[164,170,173] The pooled estimate of the RR of hip fractures from the three trials showed a significant 26% reduction in hip fractures [RR 0.74 (95% CI: 0.59; 0.94)]. Results (Figure 14) were consistent across trials (p=0.95).

Corresponding to the significant RRR of 26% for the secondary prevention of hip fractures, the absolute measures ARR and NNT of the five-year risk of hip fracture after treatment with risedronate were calculated for different levels of increasing risk, as given by the FI (Appendix 23) and for increasing age (Appendix 24). For the illustrative case of the patient with a FI of six to seven, the ARR for hip fracture was 1.0% (i.e., a reduction in risk from 3.9% to 2.9%), and the NNT was 99 (i.e., 99 patients need to be treated to avoid one hip fracture). Across the range of increasing FI risk, the ARR for hip fracture ranged from 0.1% to 2.3%, and the NNT to avoid one hip fracture ranged from 962 to 44. For the illustrative

patient in the age group 60 to 64 years, the ARR for the first hip fracture was 0.05% (i.e., a reduction in risk from 0.2% to 0.15%) and the NNT was 1,923 patients, to avoid the first fracture. The ARR and NNT for a subsequent fracture were the same. For increasing age, the five-year age-specific ARR for the first hip fracture increased from <0.05% for the youngest group (50 to 54 years old) to 5.4% in the oldest group (90+ years) and the NNT decreased from 1,923 to 18. For the subsequent fracture, ARR increased from <0.05% to 5.9%, and the NNT decreased from 1,923 to 17.

Figure 14: RR of hip fracture after risedronate (5 mg)



Wrist fractures

Wrist fractures were reported in two secondary prevention trials.[164,173] The pooled estimate of the RR of wrist fractures from the two trials showed a 33% reduction, which was not significant [RR 0.67 (95% CI: 0.42; 1.07)]. Results (Figure 15) were consistent across trials (p=0.81).

b) Additional analysis

Person-years

Results were similar for vertebral, non-vertebral, hip, and wrist fractures when using person-years (Table 12). The pooled estimates of the RR for the secondary prevention trials all showed a significant risk reduction of fracture, with the exception of wrist fractures.

Subgroup analysis

Treatment duration: No trends over years of treatments were found that deviated from the overall RR estimates (Appendix 25).

Treatment dose: For risedronate 2.5 mg, fracture data were only available for vertebral and non-vertebral sites from the secondary prevention trials (Appendices 26, 27, and 28). For vertebral fractures, the decrease in risk of fracture was significant, and there was a further albeit slight decrease in risk with the 2.5 mg dose, compared with the 5 mg dose. For non-vertebral fractures, the decrease in risk was not statistically significant, but was more pronounced with the 2.5 mg dose than the 5 mg dose.

Figure 15: RR of wrist fracture after risedronate (5 mg)

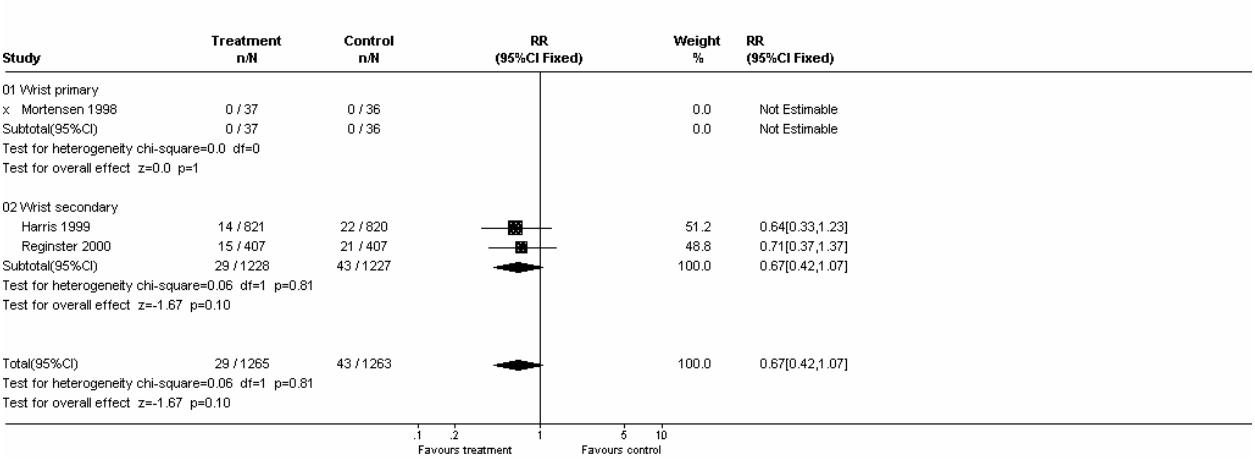


Table 12: Weighted RR of fracture after risedronate (5 mg) in person-years

Fracture Sites	Primary or Secondary Prevention	Number of Trials	Number of Participants (treatment/ control) in Person-Years	RR (95% CI)	Association p value	Heterogeneity p value
vertebral	overall	3	3,344/3,222	0.59 (0.47, 0.73)	<0.0001	0.28
	primary	1	54/58	N/E	N/E	N/E
	secondary	3	3,344/3,222	0.59 (0.47; 0.73)	<0.0001	0.28
non-vertebral	overall	4	48,564/10,884	0.49 (0.28; 0.87)*	0.01	<0.0001
	primary	0	N/A	N/A	N/A	N/A
	secondary	4	48,564/10,884	0.49 (0.28; 0.87)*	0.01	<0.0001
hip	overall	3	18,302/10,619	0.74 (0.58; 0.93)	0.01	0.98
	primary	1	54/58	N/E	N/E	N/E
	secondary	3	18,248/10,561	0.74 (0.58; 0.93)	0.01	0.98
wrist	overall	2	2,952/2,849	0.65 (0.41; 1.04)	0.07	0.83
	primary	1	54/58	N/E	N/E	N/E
	secondary	2	2,952/2,849	0.65 (0.41; 1.04)	0.07	0.83

*RR estimate based on random effects model; RR=relative risk; CI=confidence interval; N/E=not estimable; N/A=not applicable.

Sensitivity analysis

Baseline versus follow-up denominators: Using the data available for the longest treatment duration, the standard dose of risedronate (5 mg), and follow-up denominators for the number of patients in the trials, we prepared a summary of the review of fractures (Appendix 29). These data are also provided by years of treatment in Appendix 30. The pooled estimates of the RR of fracture after risedronate were similar to those obtained using the baseline denominators, with the exception that the pooled

estimate of the RR of wrist fractures from two secondary prevention trials[164,173] showed a significant reduction (39%) in wrist fractures [RR 0.61 (95% CI: 0.38; 0.96)] for risedronate 5 mg.

Random versus fixed effects model: There were instances where heterogeneity of the trial results needed a random effects model (i.e., only involving the person-years analysis). Results obtained using the random and fixed effects models were similar.

Baseline vertebral fracture rate: Appendix 31 shows a summary of the overall review of fractures using baseline vertebral fracture rates (i.e., 100%, >80%, >60%, >40%, >20%) for defining secondary prevention trials. For vertebral, non-vertebral, and wrist fractures, the pooled estimates of the RR of fracture after risedronate were similar to those obtained using the definition of secondary prevention trials with the >20% baseline fracture rate. Although the result for hip fractures became non-significant when the criteria increased from >40% to >60%, the relative risk of fracture was about the same (0.74 compared to 0.81). The confidence interval became wider because the trial by McClung *et al,*[170] with over 6,000 subjects, was excluded from the analysis.

c) Adverse events

A summary of the adverse drug reactions reported in the six randomized placebo-controlled trials of risedronate appears in Appendix 32. The reported events were similar between risedronate and placebo.

Toxicity and withdrawals

Discontinuations due to AEs or dropouts were available and analyzed for four[161,164,170,173] and five[157,161,164,170,173] risedronate trials respectively. The pooled estimate showed no statistical difference between risedronate and placebo for the risk of discontinuing medication because of AEs [RR 0.96 (95% CI: 0.88; 1.05)] or for dropouts overall [RR 0.96 (95% CI: 0.91; 1.01)]. The results were consistent across the trials.

5 ECONOMIC ANALYSIS

Our results show that there is limited evidence available to support the use of bisphosphonates for the primary prevention of fractures in women with osteoporosis. The only benefit observed was a 45% reduction in vertebral fractures associated with alendronate. As a result, an economic evaluation of the use of bisphosphonates in this clinical context is unwarranted.

Available evidence indicates that the main benefits of bisphosphonate therapy lie in the secondary prevention of osteoporotic fractures. The evidence also indicates that the magnitude of this effect varies among bisphosphonates. The effect of etidronate is limited to a 47% reduction in vertebral fractures; whereas risedronate prevents the recurrence of vertebral, non-vertebral, and hip fractures. Risedronate provides a 39% reduction in vertebral fractures, a 20% reduction in non-vertebral fractures, and a 26% reduction in hip fractures. In comparison, alendronate prevents the recurrence of all osteoporotic fractures, with reductions in vertebral (45%), non-vertebral (23%), hip (53%), and wrist (48%) fractures. For wrist fracture, the supporting evidence for alendronate is not as strong as it is for the other sites.

The differences in effect may partly explain the uptake by prescribers. In 2004, the Canadian market share of these drugs, based on utilization data provided by IMS Health (Table 2), were alendronate

(51%), risedronate (29%), and etidronate (20%). Given the disparities in treatment costs among these agents, a cost-effectiveness analysis would best quantify their relative differences regarding value for money. Such an analysis is underway at CADTH and will be published separately.

6 HEALTH SERVICES IMPACT

6.1 Impact on Population

The prevention of osteoporotic fractures is a public health intervention, particularly for hip and clinical vertebral fractures (i.e., fractures of the spine that present for medical attention). The RR of death after such fractures is six to nine times greater in postmenopausal women who are 55 to 81 years old, with low BMD. This represents a typical postmenopausal population.[9] In most cases, the mortality increase reflects poor underlying health status and comorbidity in addition to the fracture.[9] Osteoporotic fractures are associated with increase in morbidity; 50% of women who sustain a hip fracture do not return to their usual daily activities,[3] while 33% will require long-term care.[9] Reducing the incidence of such fractures can increase the quality of life of patients with osteoporosis. Such interventions may also decrease mortality. Our findings indicate that such potential benefits increase as postmenopausal women with pre-existing osteoporotic fractures advance in age. These potential health state benefits, which may be expressed in terms of utility scores, will be evaluated in a separate CADTH economic report.

6.2 Impact on Health Services

Given the morbidity consequences associated with osteoporotic fractures, preventing their recurrence can lessen the need for community-based health services (e.g., home care). It may also reduce or delay the demand for long-term care beds. However, little comparative information is available to support this.[1] Also, there is a lack of studies that evaluate the effect of bisphosphonates on hospital admissions.[1] A more detailed analysis of the impact on health services delivery, including budgetary impact, will be part of the economic report that CADTH is undertaking.

7 DISCUSSION

7.1 Summary of Results

7.1.1 Etidronate

Using data available for the longest treatment duration and baseline denominators for the number of patients in the included trials, the pooled estimate of RR of fracture after etidronate was not statistically significant for non-vertebral, hip, or wrist fractures. This was found whether etidronate was used for primary or secondary prevention. For vertebral fractures, the pooled RR estimate was significant for secondary but not for primary prevention.

The pooled analysis suggests that etidronate, when used as part of a 90-day cyclical regimen, reduces the RR of vertebral fractures by 47%. The 95% CI around this estimate is wide, and the upper

boundary representing the smallest effect consistent with the data shows an RRR of 13%. Nonetheless, a reduction in vertebral fractures is clinically important if it is associated with a reduction in pain and functional disability. Observational studies suggest that there is such an association between fractures and pain.[184-187] Furthermore, it has been recognized that women who have suffered one incident of vertebral fracture are at risk of a subsequent vertebral fracture in the following year.[188] Despite the effect on vertebral fractures, the point estimate of the effect of etidronate on non-vertebral fractures, and hip and wrist fractures individually, suggest no impact. The CIs are wide, and for non-vertebral fractures, an RRR of <32% remains possible. The wide CIs observed indicate that some uncertainty prevails around the drug's effect. A possible explanation may be that, compared to alendronate and risedronate trials, fewer (total=624) participants were recruited in etidronate trials.

Adverse effects observed in the included trials are similar between etidronate and placebo. The use of etidronate is not associated with statistically significant differences in the rate of withdrawals due to AEs [RR 0.61 (95% CI: 0.25; 1.49)] or overall withdrawals [RR 0.91 (95%CI: 0.71; 1.26)], when compared to placebo. It follows that study participants tolerated their etidronate treatment.

The results from our analysis are consistent with those of a meta-analysis by Cardona and Pastor.[189] They reported a reduction in vertebral fractures of 28.3 per 1,000 patient-years (95% CI: 26.2; 30.4); they did not derive a pooled estimate for non-vertebral fractures. This meta-analysis suggests a beneficial effect of etidronate on reducing vertebral fractures, but the data provide no support for the reduction of non-vertebral fractures.

7.1.2 Alendronate

Based on the longest treatment duration and use of baseline denominators for the number of patients in the included trials, the main benefit of alendronate was in the secondary prevention of osteoporotic fractures. At a dose of 10 mg per day, alendronate results in a statistically significant reduction in vertebral, non-vertebral, hip, and wrist fractures; the supporting evidence for wrist-fracture reduction is not as strong as for the other sites. We found that the use of alendronate 10 mg per day for the primary prevention of osteoporotic fractures is not associated with statistically significant reductions in risk, with the exception of vertebral fractures.

ADEs were similar between alendronate and placebo. There were no statistically significant differences in the rate of treatment discontinuation due to AEs [RR 0.95 (95% CI: 0.83; 1.09)] or the overall withdrawal rate [RR 1.10 (95% CI: 0.94; 1.29)] compared to placebo. We concluded that study participants tolerated their alendronate treatment.

7.1.3 Risedronate

The data available for risedronate are limited to the secondary prevention of osteoporotic fractures. Based on the longest treatment duration and the use of baseline denominators for the number of patients in each included trial, 5 mg per day risedronate was associated with a statistically significant relative reduction in each of vertebral, non-vertebral, and hip fractures. There was no statistically significant reduction in wrist fractures. The effect of risedronate on primary prevention could not be determined, because only one primary prevention trial was included in the review, and no fractures were observed.

ADEs observed with risedronate were similar to those observed with placebo. The use of risedronate was not associated with any statistically significant difference in withdrawals due to AEs [RR 0.96 (95%CI: 0.88; 1.05)] or overall withdrawals [0.96 (95% CI: 0.91; 1.01)] when compared to placebo. It was concluded that study participants tolerated their risedronate treatment.

7.1.4 Comparison with previous reviews

This review is modelled on three recently published reviews of etidronate, alendronate, and risedronate conducted, in part, by the authors of this report.[31-33] Study selection, and data extraction and analysis were redone for this review. There were four general differences in the manner that this review was conducted, compared to the three previous reviews. First, this review included articles that were published after the previous reviews were completed. Second, although published and unpublished data were used in the previous reviews, only published data were used in this review. Third, in the previous reviews, the random effects model was always used; in this review, the base analysis used the fixed effects model, unless the results were heterogeneous. Fourth, although the previous reviews considered BMD and fracture data, this review focused only on fractures, so the definition of primary and secondary prevention emphasized the fracture-study inclusion criteria. In light of these differences, we believe that this review represents research work that is independent of the three previous reviews, and that our findings complement previous findings.

a) Etidronate

For etidronate, there were three changes in the choice and classification of the included trials. First, in the previous review,[31] the trial by Watts[19] was classified as primary prevention because the average t-score was −1.7. As a result, women who were within two SD of the mean peak mass were included. Inclusion criteria restricted the population of women in the trial to those experiencing one to four previous vertebral compression fractures. As a result, the trial was classified as secondary prevention in this review. Second, for the trial by Storm,[74] additional vertebral data were obtained from the authors, but the information was not used in this review. Third, for vertebral fractures, the trials by Meunier and Pouilles[61,69] were excluded from the analysis of the previous review, because of a low incidence of vertebral fractures, but they were included in this review.

The overall results of the two reviews (i.e., primary and secondary prevention combined) were similar (Appendix 33). For primary prevention, there are differences: the RR of vertebral fracture now is >1 but with a wider CI. For non-vertebral fractures, the RR of fracture is now <1. For both reviews, these results were non-significant. For secondary prevention, the RR for vertebral fracture is now smaller and statistically significant. For non-vertebral fractures, the RR is now larger and >1 but is still non-significant.

The differences in the results for primary and secondary prevention are due to reclassifying the Watts[19] trial as secondary prevention. If this trial is considered a primary prevention trial, the primary and secondary results for the two reviews are similar. The sensitivity analysis of including and excluding unpublished data did not change the results. Including and excluding the results of the trials by Meunier and Pouilles[61,69] did not change the results.

The conclusions are similar; both reviews found no statistically significant reductions in vertebral fractures when etidronate is used for primary prevention, and no statistically significant reductions in non-vertebral fractures were observed, whether etidronate was used for primary or secondary prevention. In this review, etidronate showed a significant benefit in the secondary prevention of vertebral fractures.

b) Alendronate

For alendronate, there were four changes in the choice of the included trials. First, in the previous review,[32] additional information was obtained from the authors for the trials by McClung[170] (i.e., vertebral and non-vertebral fracture data), Hosking[116] (i.e., vertebral fracture data), Liberman[123] (i.e., separating the combined results of the two trials reported in the study), Adami[80] (i.e., specifying fracture site), and the unpublished trial by Bonnick and Rosen (i.e., unpublished non-vertebral fracture data), but this additional information was not used in this review. The trials by McClung, Adami, and Bonnick[80,92,170] were excluded from this review because "no fracture data were reported," "fracture data were reported as AEs or unspecified," and "article was unpublished" respectively. Second, the trial by Cummings[100] was classified in the previous review as secondary prevention, because the trial was originally designed to be secondary prevention with respect to the BMD (t-score <−2), despite excluding patients with fractures. Because of a shift in the norms for the young adult BMD, the t-score inclusion criteria was −1.6; as a result, the trial included patients with a BMD t-score of >−2. It was classified for this review as primary prevention, on the basis that fractures were excluded as part of the eligibility criteria, and with the new norms, the inclusion BMD criteria was t-score <−1.6. Third, the trials by Ascott-Evans[81] and Dursun[105] were included in this review, but were not published when the previous review was conducted. Fourth, we included the mixed 5 mg and 10 mg trials by Black,[84] Greenspan,[110] Cummings,[100]and Liberman,[123] and considered them as 10 mg. This allowed us to include the bulk of the data for 10 mg, and provide a conservative analysis.

It is difficult to compare the results for the two reviews, because different dose levels were selected for the analysis. An additional analysis was undertaken for this review, taking the dose ranges 5 mg to 40 mg and 10 mg to 40 mg that were used in the previous review (Appendix 34). For vertebral fractures with doses of 5 mg to 40 mg, the two reviews had nearly identical results for overall (primary and secondary prevention combined) and secondary prevention. The primary prevention for this review is significant; in the previous review, it was non-significant. This is because the classification of the large trial by Cummings[100] as a primary prevention trial led to a more precise estimate of the RR of vertebral fracture for this review. The effect on this review of excluding the trial by Cummings[100] for secondary prevention was small, because this analysis included the large Black trial.[84] For non-vertebral fractures at the 10 mg dose, the two reviews were in agreement with the significance or non-significance of the results, but the effect was generally greater in the previous review. The results for hip fracture were similar for both reviews; for wrist fractures, the previous review found a significant result, and this review had a similar RR of fracture, though the result was not significant. The inclusion of unpublished data from the previous review would have increased the precision of the estimate of the RR of wrist fracture.

The conclusions are similar in both reviews with alendronate demonstrating a benefit for primary and secondary prevention of vertebral fractures, a non-significant primary, and significant secondary prevention for non-vertebral fractures, and a benefit for overall prevention for hip fractures. For wrist fractures, the previous review found a significant result, and the current review had a similar RR of fracture, but the result was not significant.

c) Risedronate

For risedronate, there were two changes in the choice of the included trials. First, the trials by Mortensen[172] at 5 mg per day (for non-vertebral fracture data) and Clemmesen[157] at 2.5 mg per day (for vertebral and non-vertebral fracture data) were included in the previous review.[33] They were excluded from this review, because they seemed to include an off-drug treatment period (the fractures may have occurred during the follow-up period on no treatment and not during the active treatment phase of the study). Second, in the previous review, additional data were obtained from the

authors for the McClung trial,[170] but the information was not used in this review. It is possible that the abstract[169] is a subset of the paper,[170] but this could not be verified from the published reports.

The overall results combining primary and secondary prevention trials of the two reviews, were similar (Appendix 35). For the primary prevention of vertebral fractures, there was only the trial by Mortensen[172] available for analysis, and it was labelled as not estimable by Review Manager software, because no fractures occurred (i.e., zero in the numerators). This was included in the previous review by adding 0.5 to the cells to make the calculation; the result was non-significant. For the primary prevention of non-vertebral fractures, the only trial available was Mortensen.[172] The study was excluded from this review, because it included an off-drug follow-up treatment period. It was included for the previous review; and the result was non-significant. No separate results were presented in the previous review for the secondary prevention of vertebral and non-vertebral fractures. Secondary prevention of vertebral and non-vertebral fractures was not reported in the previous review, but we found similar reductions in fractures compared to this review in the graphs published in the paper.

The sensitivity analysis of including and excluding unpublished non-vertebral fracture data for the McClung[169] trial did not change the results. Including and excluding the data of the trials by Mortensen and Clemensen,[157,172] for the doses of 5 mg and 2.5 mg per day respectively, did not change the results. Mortensen's data were the only data available for the primary prevention of non-vertebral fractures.

Both reviews found that risedronate at a dose of 5 mg per day led to statistically significant reductions in vertebral and non-vertebral fractures, and for a dose of 2.5 mg per day, statistically significant reductions were observed in vertebral but not in non-vertebral fractures. Estimates of risk for primary prevention were not possible for this review, and were non-significant for the previous review. For secondary prevention, this review showed a significant fracture reduction for vertebral and non-vertebral fractures at a dose of 5 mg per day. For this review, estimates of risk for primary prevention were not possible for the 5 mg per day dose. For the previous review, the fracture reduction estimated was not significant when all doses were combined.

7.2 Study Limitations

The results of this systematic review are believed to be robust: a comprehensive literature search was performed; inclusion and exclusion criteria were specified; and a rigorous data analysis was conducted. A potential limitation of our approach may be that the update search (i.e., 2000 to 2004) did not include non-MEDLINE® indexed journals. Recent empirical evidence indicates that this approach may have introduced a risk of bias in our meta-analysis. On average, such bias is estimated to result in a ±6% variation in the pooled results.[190,191] Given that the initial literature search (i.e., 1966 to 2000) was extensive, any impact of only using MEDLINE® for the search update is expected to be minimal. This was confirmed by a parallel literature search update (i.e., 1999 to July 2004) that was conducted for the upcoming CADTH economic report. The search update included etidronate, alendronate, and risedronate (daily dose regimen only) in addition to teriparatide. Several databases were searched (i.e., MEDLINE®, EMBASE®, BIOSIS Previews®, ToxFile, PubMed, and the Cochrane Library) and no additional articles meeting the inclusion criteria were identified.

While our methods are robust, the results of our meta-analysis are only as strong as the primary studies included. The limitations regarding study quality were fracture assessment and classification, the lack of clarity of the concealment of allocation, and large losses to follow-up.

A potential source of heterogeneity is the lack of a uniform definition of non-vertebral fracture. While some researchers use a liberal definition (any fracture other than vertebral fracture), others use a more conservative definition that includes only fractures of the hip, clavicle, humerus, wrist, pelvis, or leg.[192] The statistical power to detect heterogeneity was limited for some tests, because of the low number of fractures in some categories. Another consideration is the fact that fracture data were not the primary outcome for many trials. In particular, none of the 11 etidronate trials, three[84,100,105] of the 11 alendronate trials, and three[164,170,173] of the six risedronate trials had fractures as the primary outcome. Other sources of heterogeneity and possible bias, related to some secondary prevention studies, are the inclusion of participants with a low BMD but no proven fractures, and the difficulty in discriminating between traumatic and pathological fracture types. Also, at times, our criteria for categorizing a study as a secondary prevention trial differed from those used by study investigators. An example is the study by McClung *et al.,*[170] which included two age groups. In our review, we considered that both groups evaluated the effect of risedronate in secondary prevention of osteoporotic fractures; although study investigators may not have intended the same. Both groups satisfied two of our secondary prevention criteria, i.e., baseline fracture rate and age. Both groups had a baseline fracture rate >20% (primary prevention studies were required to have a baseline fracture rate of <20%). Study participants in both groups were >62 years of age (we considered a trial as secondary prevention if the average age was >62 years). Finally, the exploration of differences in effect between primary and secondary prevention trials was a concern in our review.

Another limitation is that the approach used for concealment of treatment allocation was not reported for most trials (i.e., classified as "unclear"). For etidronate, concealed allocation was unclear for all 11 trials; for alendronate, three[89,100,116] of the 11 trials concealed allocation; and for the remainder, it was unclear. For risedronate, treatment allocation was concealed in one trial,[164] and was unclear for the other five trials.

An additional limitation is the length of follow-up in the studies. It is difficult to extrapolate beyond the duration of the follow-up trials in the review with respect to the long-term impact on fractures. Data from longer term trials will help establish if the effect on fractures is maintained, increased, or diminished. Another limitation is that male patients with osteoporosis were not part of the included studies. Given that there are twice as many women with osteoporosis in Canada compared to men, our report will be relevant to Canadian decision makers.

The approach that we used to evaluate the effect of bisphosphonates over time may result in some estimates that are not robust. In particular, to determine the effect on the five-year risk of fracture, we based our evaluation on the FI by Black *et al.,*[35] and for lifetime and five-year age-specific risks, we used an existing model from Doherty *et al.*[36] Although the latter approach allowed us to estimate the variation in risks between younger and older postmenopausal women; these estimates may be associated with uncertainty. We believe that this information may be useful to decision makers.

In addition to the recommended doses, we evaluated subtherapeutic doses (e.g., alendronate 5 mg daily and risedronate 2.5 mg daily). We included such trials, not only to strengthen our conclusions and include earlier classical studies, but to consider doses that some believe are efficacious. In our review, the results for 2.5 mg of risedronate and 5 mg alendronate could generate hypotheses for future research. These were only considered as secondary analyses. Second, although some studies

did not report on the use of calcium supplements, we assumed that most study participants (and most women with osteoporosis) would use supplementation. We believe that this assumption is reasonable. Finally, for some of the secondary analyses that we performed, such as the baseline versus follow-up denominators and the person-years analyses, we assumed a linear drop-out rate. Although discontinuation of treatment may vary, we favoured this approach, because it required fewer assumptions. It was applied equally to all comparisons to limit the introduction of bias.

A limitation of evaluating data on adverse effects from summary meta-analyses is that participants in RCTs tend to be healthier with fewer comorbid diseases. As a result, it may be impossible to generalize the results for clinical practice. Patients with pre-existing gastrointestinal (GI) disorders were excluded in some trials. For etidronate, two[19,64] of the 11 trials excluded these patients (an additional trial[68] possibly excluded GI patients, where it is indicated that patients were excluded for "any condition contraindicating study medication"). For alendronate, eight[84,89,100,105,108,116,123,130] of 11 trials excluded GI patients. None of the six risedronate trials excluded these patients. Furthermore, RCTs are underpowered for rare effects, and meta-analyses of these trials cannot provide conclusive information pertaining to drug toxicity. The heterogeneity of the ADEs reported in the RCTs – including their nature, low occurrence, and the way that they were assessed by investigators – made these improper for meta-analysis. Finally, because RCTs are not designed to measure ADEs, particularly rare ones, it is common practice to include sources of information other than RCTs. While some reviewers include ADEs reported in observational studies, we elected to obtain information from the Canadian Adverse Drug Reaction Monitoring Program (CADRMP). This choice was made, because we wanted to reflect Canadian data.

7.3 Generalized Findings

Our ability to generalize our findings is limited by the controlled design of the trials included in our review. Study participants were carefully selected in these trials, but the use of the drugs in real life may vary from study conditions. Study participants were observed for periods varying from one to four years. While our results provide support for efficacy (i.e., can the intervention have an effect on outcome?), they may only provide partial information on the long-term effectiveness of bisphosphonates in preventing osteoporotic fractures (i.e., does the intervention have an effect on outcome?).

We could not find any statistically significant differences in the rates of ADEs or withdrawal rates due to ADEs between patients receiving a bisphosphonate or patients receiving a placebo. Outside of controlled trials, concerns exist regarding the safe use of these drugs, especially alendronate, and to a lesser extent, risedronate, for which esophageal ulcers and gastritis have been reported.[193] While such AEs have been identified mainly through case reports and endoscopic studies, similar concerns are reflected in the proportions of GI adverse drug reactions associated with the use of bisphosphonates reported to the CADRMP.[194-196] The adverse GI drug reactions represented 38% of all reactions reported for alendronate, 35% for risedronate, and 18% for etidronate (Appendix 36). These proportions should be interpreted cautiously as adverse drug reactions are reported to CADRMP on a volunteer basis by health professionals, and reactions may be unreported. It is estimated that <10% of adverse reactions are reported to Health Canada.[197] A definite cause and effect relation has not been established for these adverse drug reactions. This uncontrolled information does support recommendations for the appropriate administration of medication (i.e., swallowing each tablet with a full glass of water, and not lying down for at least 30 minutes), and suggests contraindications may not have been respected in practice.[193] Some trials included in our review excluded patients with

pre-existing upper GI problems. We agree with Kherani *et al.*[193] that patient education and directions for the correct administration of bisphosphonates (i.e., particularly alendronate, and to a lesser degree, risedronate) are key to ensuring safe use.

7.4 Knowledge Gaps

Some clinical trials with bisphosphonates[85,164,170] suggest that their effect in reducing non-vertebral fractures may be greater in patients with lower BMD who start treatment. The existing data have not resolved whether differences in risk reduction exist across groups of patients with varying degrees of osteoporosis. The impact of bisphosphonates on the RR of non-vertebral fractures in populations without osteoporosis also merits further investigation. Additional research is needed to clarify the role of risedronate in the primary prevention of osteoporotic fractures. Finally, areas of future research should focus on issues such as whether bisphosphonates reduce non-vertebral fractures in younger women, and if supplemental calcium or combination therapy with other active treatment can significantly increase the effect of these drugs on fractures.

8 CONCLUSIONS

Overall evidence varies, depending on the bisphosphonate. For etidronate, most trials enrolled a small number of participants and were not necessarily designed to measure fractures, which limits our findings. Available evidence for alendronate and risedronate is more robust. Acknowledging the available evidence, we conclude that the main benefit of the three bisphosphonates available on the Canadian market for the management of osteoporotic fractures, is the secondary prevention of such fractures.

- Etidronate, used at 400 mg per day, showed a main benefit in the secondary prevention of vertebral fractures. There were no statistically significant reductions in vertebral fractures when used for primary prevention. No statistically significant reductions in non-vertebral, hip, or wrist fractures were observed, whether etidronate was used for primary or secondary prevention.
- Alendronate showed a main benefit in the secondary prevention of all osteoporotic fractures. At a dose of 10 mg per day, statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were observed. There were no statistically significant reductions found for the primary prevention of osteoporotic fractures, with the exception of vertebral fractures.
- Risedronate demonstrated a main benefit in the secondary prevention of most osteoporotic fractures. At a dose of 5 mg per day, statistically significant reductions in vertebral, non-vertebral, and hip fractures were observed (but not for wrist). Estimates of risk for primary prevention were not possible, because only one trial was included in the review, and no fractures were observed.

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APPENDICES

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