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Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women (Review)

Wells GA, Hsieh SC, Peterson J, Zheng C, Kelly SE, Shea B, Tugwell P

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 10
OBJECTIVES 11
METHODS 11
Figure 1. 12
RESULTS 17
Figure 2. 18
Figure 3. 23
Figure 4. 24
DISCUSSION 30
AUTHORS' CONCLUSIONS 33
ACKNOWLEDGEMENTS 33
REFERENCES 34
CHARACTERISTICS OF STUDIES 39
DATA AND ANALYSES 97
Analysis 1.1. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 1: Clinical vertebral fractures 99
Analysis 1.2. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 2: Non-vertebral fractures .. 100
Analysis 1.3. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 3: Hip fractures 101
Analysis 1.4. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 4: Wrist fractures 101
Analysis 1.5. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 5: Radiographic vertebral fractures 102
Analysis 1.6. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 6: Withdrawals due to adverse events 103
Analysis 1.7. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 7: Serious adverse events ... 104
Analysis 1.8. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 8: Gastrointestinal adverse events 104
Analysis 1.9. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 9: Atypical femoral fractures 105
Analysis 2.1. Comparison 2: Etidronate 400 mg/day versus placebo - subgroup of 1-year studies, Outcome 1: Radiographic vertebral fractures 106
Analysis 3.1. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 1: Clinical vertebral fractures 107
Analysis 3.2. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 2: Non-vertebral fractures 107
Analysis 3.3. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 3: Hip fractures 108
Analysis 3.4. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 4: Radiographic vertebral fractures 108
Analysis 4.1. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 1: Non-vertebral fractures 109
Analysis 4.2. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 2: Hip fractures 110
Analysis 4.3. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 3: Wrist fractures ... 110
Analysis 4.4. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 4: Radiographic vertebral fractures 111
Analysis 5.1. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 1: Non-vertebral fractures 112
Analysis 5.2. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 2: Hip fractures 112
Analysis 5.3. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 3: Wrist fractures ... 113
Analysis 5.4. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 4: Radiographic vertebral fractures 113
Analysis 6.1. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 1: Clinical vertebral fractures 114

Analysis 6.2. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 2: Non-vertebral fractures 115
Analysis 6.3. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 3: Hip fractures 115
Analysis 6.4. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 4: Wrist fractures 116
Analysis 6.5. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 5: Radiographic vertebral fractures 116
Analysis 7.1. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 1: Clinical vertebral fractures 117
Analysis 7.2. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 2: Non-vertebral fractures 118
Analysis 7.3. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 3: Hip fractures 119
Analysis 7.4. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 4: Wrist fractures 119
Analysis 7.5. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 5: Radiographic vertebral fractures 120
Analysis 8.1. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 1: Non-vertebral fractures 121
Analysis 8.2. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 2: Hip fractures 122
Analysis 8.3. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 3: Wrist fractures 122
Analysis 8.4. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 4: Radiographic vertebral fractures 123
Analysis 9.1. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 1: Clinical vertebral fractures 124
Analysis 9.2. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 2: Non-vertebral fractures 125
Analysis 9.3. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 3: Hip fractures 125
Analysis 9.4. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 4: Wrist fractures 126
Analysis 9.5. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 5: Radiographic vertebral fractures 126
Analysis 10.1. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 1: Clinical vertebral fractures 128
Analysis 10.2. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 2: Non-vertebral fractures 128
Analysis 10.3. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 3: Hip fractures 129
Analysis 10.4. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 4: Wrist fractures 129
Analysis 10.5. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 5: Radiographic vertebral fractures 130
Analysis 11.1. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 1: Hip fractures 131
Analysis 11.2. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 2: Wrist fractures 131
Analysis 11.3. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 3: Radiographic vertebral fractures 132
Analysis 11.4. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 4: Withdrawals due to adverse events 132
Analysis 11.5. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 5: Serious adverse events 133
Analysis 11.6. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 6: Gastrointestinal adverse events 133

Analysis 11.7. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 7: Atypical femoral fractures 134
Analysis 12.1. Comparison 12: Etidronate 200 mg/day versus placebo - subgroup of 1-year studies, Outcome 1: Radiographic vertebral fractures 134
Analysis 13.1. Comparison 13: Etidronate 200 mg/day versus placebo - subgroup of 2-year studies, Outcome 1: Hip fractures 135
Analysis 13.2. Comparison 13: Etidronate 200 mg/day versus placebo - subgroup of 2-year studies, Outcome 2: Wrist fractures 136
Analysis 13.3. Comparison 13: Etidronate 200 mg/day versus placebo - subgroup of 2-year studies, Outcome 3: Radiographic vertebral fractures 136
Analysis 14.1. Comparison 14: Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 1: Hip fractures 137
Analysis 14.2. Comparison 14: Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 2: Wrist fractures 137
Analysis 14.3. Comparison 14: Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 3: Radiographic vertebral fractures 138
Analysis 15.1. Comparison 15: Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 1: Hip fractures 139
Analysis 15.2. Comparison 15: Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 2: Wrist fractures 139
Analysis 15.3. Comparison 15: Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 3: Radiographic vertebral fractures 140
Analysis 16.1. Comparison 16: Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 1: Hip fractures 141
Analysis 16.2. Comparison 16: Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 2: Wrist fractures 141
Analysis 16.3. Comparison 16: Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 3: Radiographic vertebral fractures 142
Analysis 17.1. Comparison 17: Clinical vertebral fractures, Outcome 1: Treatment versus reference, secondary 143
Analysis 18.1. Comparison 18: Non-vertebral fractures, Outcome 1: Treatment versus reference, secondary 145
Analysis 19.1. Comparison 19: Hip fractures, Outcome 1: Treatment versus reference, secondary 148
Analysis 20.1. Comparison 20: Wrist fractures, Outcome 1: Treatment versus reference, secondary 150
Analysis 21.1. Comparison 21: Radiographic vertebral fractures, Outcome 1: Treatment versus reference, secondary 153
Analysis 22.1. Comparison 22: Withdrawals due to adverse events, Outcome 1: Treatment versus reference, primary 157
Analysis 22.2. Comparison 22: Withdrawals due to adverse events, Outcome 2: Treatment versus reference, secondary 158
Analysis 23.1. Comparison 23: Serious adverse events, Outcome 1: Treatment versus reference, secondary 161
Analysis 24.1. Comparison 24: Gastrointestinal adverse events, Outcome 1: Treatment versus reference, secondary 163
Analysis 25.1. Comparison 25: Atypical femoral fracture, Outcome 1: Treatment versus reference, secondary 165
ADDITIONAL TABLES 167
APPENDICES 175
WHAT'S NEW 207
HISTORY 207
CONTRIBUTIONS OF AUTHORS 207
DECLARATIONS OF INTEREST 208
SOURCES OF SUPPORT 208
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 208
NOTES 208
INDEX TERMS 209

[Intervention Review]

Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women

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ABSTRACT

Background

Osteoporosis is an abnormal reduction in bone mass and bone deterioration, leading to increased fracture risk. Etidronate belongs to the bisphosphonate class of drugs which act to inhibit bone resorption by interfering with the activity of osteoclasts – bone cells that break down bone tissue. This is an update of a Cochrane review first published in 2008. For clinical relevance, we investigated etidronate's effects on postmenopausal women stratified by fracture risk (low versus high).

Objectives

To assess the benefits and harms of intermittent/cyclic etidronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women at lower and higher risk of fracture, respectively.

Search methods

We searched the Cochrane Central Register of Control Trials (CENTRAL), MEDLINE, Embase, two clinical trial registers, the websites of drug approval agencies, and the bibliographies of relevant systematic reviews. We identified eligible trials published between 1966 and February 2023.

Selection criteria

We included randomized controlled trials that assessed the benefits and harms of etidronate in the prevention of fractures for postmenopausal women. Women in the experimental arms must have received at least one year of etidronate, with or without other anti-osteoporotic drugs and concurrent calcium/vitamin D. Eligible comparators were placebo (i.e. no treatment; or calcium, vitamin D, or both) or another anti-osteoporotic drug. Major outcomes were clinical vertebral, non-vertebral, hip, and wrist fractures, withdrawals due to adverse events, and serious adverse events. We classified a study as secondary prevention if its population fulfilled one or more of the following hierarchical criteria: a diagnosis of osteoporosis, a history of vertebral fractures, a low bone mineral density T-score (≤ -2.5), or aged 75 years or older. If none of these criteria were met, we considered the study to be primary prevention.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The review has three main comparisons: (1) etidronate 400 mg/day versus placebo; (2) etidronate 200 mg/day versus placebo; (3) etidronate at any dosage versus another anti-osteoporotic agent. We stratified the analyses for each comparison into primary and secondary prevention studies. For major outcomes in the placebo-controlled studies of etidronate 400 mg/day, we followed our original review by defining a greater than 15% relative change as clinically important. For all outcomes of interest, we extracted outcome measurements at the longest time point in the study.

Main results

Thirty studies met the review's eligibility criteria. Of these, 26 studies, with a total of 2770 women, reported data that we could extract and quantitatively synthesize. There were nine primary and 17 secondary prevention studies.

We had concerns about at least one risk of bias domain in each study. None of the studies described appropriate methods for allocation concealment, although 27% described adequate methods of random sequence generation. We judged that only 8% of the studies avoided performance bias, and provided adequate descriptions of appropriate blinding methods. One-quarter of studies that reported efficacy outcomes were at high risk of attrition bias, whilst 23% of studies reporting safety outcomes were at high risk in this domain.

The 30 included studies compared (1) etidronate 400 mg/day to placebo (13 studies: nine primary and four secondary prevention); (2) etidronate 200 mg/day to placebo (three studies, all secondary prevention); or (3) etidronate (both dosing regimens) to another anti-osteoporotic agent (14 studies: one primary and 13 secondary prevention). We discuss only the etidronate 400 mg/day versus placebo comparison here.

For primary prevention, we collected moderate- to very low-certainty evidence from nine studies (one to four years in length) including 740 postmenopausal women at lower risk of fractures. Compared to placebo, etidronate 400 mg/day probably results in little to no difference in non-vertebral fractures (risk ratio (RR) 0.56, 95% confidence interval (CI) 0.20 to 1.61); absolute risk reduction (ARR) 4.8% fewer, 95% CI 8.9% fewer to 6.1% more) and serious adverse events (RR 0.90, 95% CI 0.52 to 1.54; ARR 1.1% fewer, 95% CI 4.9% fewer to 5.3% more), based on moderate-certainty evidence. Etidronate 400 mg/day may result in little to no difference in clinical vertebral fractures (RR 3.03, 95% CI 0.32 to 28.44; ARR 0.02% more, 95% CI 0% fewer to 0% more) and withdrawals due to adverse events (RR 1.41, 95% CI 0.81 to 2.47; ARR 2.3% more, 95% CI 1.1% fewer to 8.4% more), based on low-certainty evidence. We do not know the effect of etidronate on hip fractures because the evidence is very uncertain (RR not estimable based on very low-certainty evidence). Wrist fractures were not reported in the included studies.

For secondary prevention, four studies (two to four years in length) including 667 postmenopausal women at higher risk of fractures provided the evidence. Compared to placebo, etidronate 400 mg/day may make little or no difference to non-vertebral fractures (RR 1.07, 95% CI 0.72 to 1.58; ARR 0.9% more, 95% CI 3.8% fewer to 8.1% more), based on low-certainty evidence. The evidence is very uncertain about etidronate's effects on hip fractures (RR 0.93, 95% CI 0.17 to 5.19; ARR 0.0% fewer, 95% CI 1.2% fewer to 6.3% more), wrist fractures (RR 0.90, 95% CI 0.13 to 6.04; ARR 0.0% fewer, 95% CI 2.5% fewer to 15.9% more), withdrawals due to adverse events (RR 1.09, 95% CI 0.54 to 2.18; ARR 0.4% more, 95% CI 1.9% fewer to 4.9% more), and serious adverse events (RR not estimable), compared to placebo. Clinical vertebral fractures were not reported in the included studies.

Authors' conclusions

This update echoes the key findings of our previous review that etidronate probably makes or may make little to no difference to vertebral and non-vertebral fractures for both primary and secondary prevention.

PLAIN LANGUAGE SUMMARY

Does etidronate prevent fractures caused by osteoporosis in postmenopausal women?

Key messages

- For women with close to normal bone density (bone strength) and no previous broken spinal bones, etidronate probably makes little or no difference to the likelihood of having a hip or wrist fracture or a serious adverse (unwanted/harmful) event.
- For women who have low bone density and are at risk for or have had a previous broken spinal bone, etidronate may make little or no difference in preventing fractures in bones other than the spine.

What is osteoporosis?

Bone is a living, growing part of your body. Throughout your lifetime, new bone cells grow, and old bone cells break down to make room for new, stronger bone. When you have osteoporosis, the old bone breaks down faster than the new bone can replace it. As this happens, the bones lose minerals (such as calcium). This makes bones weaker and more likely to break, even after a minor injury, such as a slight bump or fall. Women who have gone through menopause are more likely to get osteoporosis than other people.

What is etidronate?

Etidronate belongs to the class of medicines called bisphosphonates, which slow down the cells that break down the old bone. It is given by mouth in an intermittent or cyclical schedule; for example, a 400 mg tablet daily for two weeks every 90 days, followed by calcium or no treatment for the remainder of each 90-day treatment cycle.

What did we want to find out?

We wanted to find out if etidronate was better than placebo (inactive or 'dummy' medicine) or another medicine for osteoporosis in preventing broken bones in postmenopausal women. For clinical relevance, we looked at etidronate's effects on women, as grouped by their risk of fracture (lower versus higher risk). We also wanted to find out if etidronate was associated with any unwanted effects.

What did we do?

We searched for studies comparing etidronate to placebo or another medicine for preventing osteoporosis. We compared and summarized their results, and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

Overall, we found 30 studies, but 4 studies provided insufficient information about their results. Thus, we were able to analyse the results of 26 studies involving 2770 women. Nine studies were interested in 'primary prevention' of osteoporosis-based fractures, meaning they focused on women at lower fracture risk, who had bones with near-to-normal density/strength and no previous broken spinal bones. Seventeen studies were interested in 'secondary prevention' with etidronate, meaning they focused on women at higher fracture risk, who already had weak bones (low bone density), had a broken spinal bone, or both. Most studies mainly included white women. The studies lasted between 1 and 4 years. Some studies gave the women 400 mg/day of etidronate, whilst other studies gave 200 mg/day.

Main results for primary prevention studies that gave women 400 mg of etidronate/day

Compared to a placebo, etidronate:

• probably makes little or no difference to non-vertebral (non-spinal) fractures and serious adverse events;

• may make little or no difference to clinical vertebral fractures (that is, spinal fractures suggested by clinical signs and symptoms) and the number of women who left the studies due to adverse events.

The evidence is very uncertain about the effect of etidronate on hip fractures. None of the studies reported on the effect on wrist fractures.

Main results for secondary prevention studies that gave women 400 mg of etidronate/day

Compared to a placebo, etidronate may make little or no difference in preventing fractures in bones other than the spine. The evidence is very uncertain about the effect of etidronate on hip and wrist fractures, the number of women who left the studies due to adverse events, and serious adverse events. None of the studies reported on etidronate's effect on clinical vertebral fractures.

What are the limitations of the evidence?

Our confidence in the evidence ranged from very low to moderate. In general, we have little confidence in the evidence because it is possible that the women in the studies were aware of which treatment they were getting, which could influence the results, and because many of the studies were very small.

How up to date is this evidence?

The evidence is current to February 2023.

Summary of findings 1. Intermittent/cyclic etidronate 400 mg/day compared to placebo for the primary prevention of osteoporotic fractures in postmenopausal women

Intermittent/cyclic etidronate 400 mg/day compared to placebo for the primary prevention of osteoporotic fractures in postmenopausal women

Patient or population: postmenopausal women with a lower risk for fractures[a]
Setting: outpatients
Intervention: intermittent/cyclic[b] etidronate 400 mg/day for at least one year
Comparison: placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens†
		Without etidronate 400 mg/day	With etidronate 400 mg/day	Difference		
Clinical vertebral fractures assessed with: participant's clinical signs and symptoms Follow-up: 2 years № of participants: 163 (2 RCTs)	RR 3.03 (0.32 to 28.44)	Study population			⊕⊕⊖⊖ **Low**[e]	Etidronate 400 mg/day may result in little to no difference in clinical vertebral fractures.
		0.0%	0.02% (0 to 0)	0.02% more (0 fewer to 0 more)		
		Low-risk population				
		1.2%[c]	3.6% (0.4 to 34.1)	2.4% more (0.8 fewer to 32.9 more)		
		Moderate-risk population				
		5.3%[d]	16.1% (1.7 to 100)	10.8% more (3.6 fewer to 145.4 more)		
Non-vertebral fractures assessed with: participant's clinical signs and symptoms Follow-up: 2 years № of participants: 163 (2 RCTs)	RR 0.56 (0.20 to 1.61)	Study population			⊕⊕⊕⊖ **Moderate**[f]	Etidronate 400 mg/day probably results in little to no difference in non-vertebral fractures.
		11.0%	6.1% (2.1 to 17.1)	4.8% fewer (8.9 fewer to 6.1 more)		
		Low-risk population				
		8.6%[c]	4.8%	3.8% fewer		

			(1.6 to 13.4)	(7 fewer to 4.8 more)		
		Moderate-risk population				
		16.5%[d]	9.2% (3.1 to 25.7)	7.3% fewer (13.4 fewer to 9.2 more)		
Hip fractures assessed with: participant's clinical signs and symptoms № of participants: 189 (2 RCTs)	Not estimable	Study population			⊕⊖⊖⊖ **Very low**[e,g]	Zero hip fractures were reported, and the effect size was not estimable. The evidence is very uncertain about the effect of etidronate 400 mg/day on hip fractures.
		0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)		
		Low-risk population				
		0.4%[c]	0.0% (0 to 0)	0.4% fewer (0.4 fewer to 0.4 fewer)		
		Moderate-risk population				
		1.9%[d]	0.0% (0 to 0)	1.9% fewer (1.9 fewer to 1.9 fewer)		
Wrist fractures № of participants: 0 (0 RCTs)	Not reported	Study population			NA	Wrist fractures were not measured/reported in the included studies.
		NA	NA	NA		
Withdrawals due to adverse events assessed with: participant's clinical signs and symptoms Follow-up: range 1 to 4 years № of participants: 628 (8 RCTs)	RR 1.41 (0.81 to 2.47)	Study population			⊕⊕⊖⊖ **Low**[f,g]	Etidronate 400 mg/day may result in little to no difference in withdrawals due to adverse events.
		5.7%	8.0% (4.6 to 14)	2.3% more (1.1 fewer to 8.4 more)		
Serious adverse events assessed with: participant's clinical signs and symptoms Follow -up: 2 years № of participants: 497 (5 RCTs)	RR 0.90 (0.52 to 1.54)	Study population			⊕⊕⊕⊖ **Moderate**[f,h]	Etidronate 400 mg/day probably results in little to no difference in serious adverse events.
		10.0%	8.9% (5.1 to 15.2)	1.1% fewer (4.9 fewer to 5.3 more)		

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

†__Both the importance and certainty__ of the supporting evidence are taken into account. For importance, a > 15% relative change together with precision is defined as “clinically important” (Wells 2008a). We use the terms "increase", "decrease", or "no difference" when the certainty of the evidence is high. The terms "probably”, “may”, and “don’t know/uncertain” are used when the certainty of the evidence is “moderate”, “low”, or “very low”, respectively (Santesso 2020; Schünemann 2022a).

CI: confidence interval; **NA:** not available; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

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

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[a]Postmenopausal women who did not fulfil any of the hierarchical criteria: a diagnosis of osteoporosis, a history of vertebral fractures, bone mineral density T-score ≤ -2.5, or age ≥ 75 years old.
[b]Etidronate is given orally on an intermittent/cyclical schedule, e.g. 400 mg for two weeks every 90 days, followed by calcium or no treatment for the remainder of each 90-day treatment cycle.
[c]Assumed 'low risk' with placebo was derived from the quintile of the FRACTURE Index (FI) score 1-2, where the 5-year risk of vertebral, non-vertebral and hip fracture is 1.2%, 8.6%, and 0.4%, respectively (Black 2001).
[d]Assumed 'moderate risk' with placebo was derived from the quintile of the FRACTURE Index (FI) score 5, where the 5-year risk of vertebral, non-vertebral, and hip fracture is 5.3%, 16.5%, and 1.9%, respectively (Black 2001).
[e]There are very few events and the confidence intervals around both relative and absolute estimates of effect include both appreciable benefit and appreciable harm. Downgraded two levels for imprecision.
[f]Both the total number of events and sample size are smaller than what are needed to meet the optimal information size (OIS). Downgraded one level for imprecision.
[g]Evidence was estimated from studies judged to be at high risk in the domains of performance bias and/or attrition bias. These studies carried a moderate weight of the evidence and the impact was considered serious. Downgraded one level for risk of bias (ROB).
[h]Evidence was estimated from studies judged to be at high risk of performance and attrition bias. However, the studies carried a very small weight of the evidence and the impact was considered not serious. Not downgraded for ROB.

Summary of findings 2. Intermittent/cyclic etidronate 400 mg/day compared to placebo for the secondary prevention of osteoporotic fractures in postmenopausal women

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Intermittent/cyclic etidronate 400 mg/day compared to placebo for the secondary prevention of osteoporotic fractures in postmenopausal women

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Patient or population: postmenopausal women with a higher risk for fractures[a]
Setting: outpatients
Intervention: intermittent/cyclic[b] etidronate 400 mg/day for at least one year
Comparison: placebo/no treatment

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens†
		Without etidronate 400 mg/day	With etidronate 400 mg/day	Difference		
Clinical vertebral fractures № of participants: 0 (0 RCTs)	Not reported	Study population			NA	Clinical vertebral fractures were not measured/reported in the included studies.
		NA	NA	NA		
Non-vertebral fractures assessed with: participant's clinical signs and symptoms Follow-up: range 2 to 4 years № of participants: 598 (4 RCTs)	RR 1.07 (0.72 to 1.58)	Study population			⊕⊕⊖⊖ **Low**[e,f,g]	Etidronate 400 mg/day may result in little to no difference in non-vertebral fractures.
		13.5%	14.4% (9.2 to 20.5)	0.9% more (3.8 fewer to 8.1 more)		
		Moderate-risk population				
		16.5%[c]	17.7% (11.9 to 26.4)	1.2% more (4.6 fewer to 9.9 more)		
		High-risk population				
		27.5%[d]	29.4% (19.8 to 44)	1.9% more (7.7 fewer to 16.5 more)		
Hip fractures assessed with: participant's clinical signs and symptoms Follow-up: range 2 to 4 years № of participants: 283 (2 RCTs)	RR 0.93 (0.17 to 5.19)	Study population			⊕⊖⊖⊖ **Very low**[h,i,j]	The evidence is very uncertain about the effect of etidronate 400 mg/day on hip fractures.
		1.4%	1.4% (0.2 to 7.6)	0.0% fewer (1.2 fewer to 6.3 more)		
		Moderate-risk population				
		1.9%[c]	1.9% (0.3 to 10.4)	0.0% fewer (1.6 fewer to 8.5 more)		
		High-risk population				
		8.7%[d]	8.7% (1.5 to 47.9)	0.0% fewer		

				(7.2 fewer to 39.1 more)		
Wrist fractures assessed with: participant's clinical signs and symptoms Follow-up: range 3 to 4 years № of participants: 140 (2 RCTs)	RR 0.90 (0.13 to 6.04)	Study population			⊕⊖⊖⊖ **Very low**[h,i,j]	The evidence is very uncertain about the effect of etidronate 400 mg/day on wrist fractures.
		2.9%	2.9% (0.4 to 18.8)	0.0% fewer (2.5 fewer to 15.9 more)		
Withdrawals due to adverse events assessed with: participant's clinical signs and symptoms Follow-up: range 2 to 4 years № of participants: 624 (4 RCTs)	RR 1.09 (0.54 to 2.18)	Study population			⊕⊖⊖⊖ **Very low**[f,k,l]	The evidence is very uncertain about the effect of etidronate 400 mg/day on withdrawals due to adverse events.
		4.2%	4.5% (2.3 to 9.1)	0.4% more (1.9 fewer to 4.9 more)		
Serious adverse events assessed with: participant's clinical signs and symptoms Follow-up: 48 months № of participants: 100 (1 RCT)	Not estimable	Study population			⊕⊖⊖⊖ **Very low**[h,i,m]	Zero serious adverse events were reported, and the effect size was not estimable. The evidence is very uncertain about the effect of etidronate 400 mg/day on serious adverse events.
		0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
†__Both the importance andcertainty__ of the supporting evidence are taken into account. For importance, a > 15% relative change together with precision is defined as “clinically important” (Wells 2008a). We use the terms "increase", "decrease", or "no difference" when the certainty of the evidence is high. The terms “probably”, “may”, and “don’t know/uncertain” are used when the certainty of the evidence is “moderate”, “low”, or “very low”, respectively (Santesso 2020; Schünemann 2022a).

CI: confidence interval; **NA:** not available; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[a]Postmenopausal women who fulfilled at least one of the hierarchical criteria: a diagnosis of osteoporosis, a history of vertebral fractures, a bone mineral density T-score ≤ -2.5, and age ≥ 75 years old.

[b]Etidronate is given orally on an intermittent/cyclical schedule, e.g. 400 mg for two weeks every 90 days, followed by calcium or no treatment for the remainder of each 90-day treatment cycle.

[c]Assumed 'moderate risk' with placebo was derived from the quintile of the FRACTURE Index (FI) score 5, where the 5-year risk of vertebral, non-vertebral, and hip fracture is 5.3%, 16.5% and 1.9%, respectively (Black 2001).

[d]Assumed 'high risk' with placebo was derived from the quintile of the FRACTURE Index (FI) score 8-13, where the 5-year risk of vertebral, non-vertebral, and hip fracture is 11.2%, 27.5% and 8.7%%, respectively (Black 2001).

[e]Evidence was estimated from studies judged to be at high risk in performance and/or attrition bias. However, the studies carried a small weight and the impact was not considered serious. Not downgraded for risk of bias (ROB).

[f]Both the total number of events and the sample size did not meet the optimal information size (OIS) criterion. Downgraded one level for imprecision.

[g]Evidence was estimated from studies which applied an ADFR regimen (activation, depression, treatment-free, repeat) and used an activator before etidronate. These studies carried less than half the weight of the evidence, without which only the magnitude of the effect size (in the sensitivity analysis excluding studies applying an ADFR regimen) was slightly changed. Downgraded one level for indirectness.

[h]Evidence was estimated from studies that applied the ADFR regimen (activation, depression, treatment-free, repeat) and administered an activator before etidronate. These studies carried a moderate to large weight of the evidence (52% to 100%), without which the estimated effect size was changed noticeably (in the sensitivity analysis excluding studies using an ADFR regimen). The estimated effects of etidronate were likely to be influenced. Downgraded two levels for indirectness.

[i]Evidence was estimated from studies judged to be at high risk of performance, detection and/or attrition bias. These studies carried a great weight of the evidence and the impact was considered very serious. Downgraded two levels for ROB.

[j]There were very few events and the confidence intervals around both relative and absolute estimates of effect include both appreciable benefit and appreciable harm. Downgraded two levels for imprecision.

[k]Evidence was mainly estimated from a study judged to be at high risk of attrition bias and selective reporting, and a study at high risk of bias in the blinding domain. The impact was considered very serious, so we downgraded two levels for ROB.

[l]Evidence was estimated from studies that applied the ADFR regimen (activation, depression, treatment-free, repeat) and used an activator before etidronate. However, these studies carried a small weight of the evidence, and were less likely to bias the outcome measures. Not downgraded for indirectness.

[m]Zero events were reported in the included studies for which the sample size was insufficient to meet the optimal information size (OIS). Downgraded two levels for imprecision.

BACKGROUND

Description of the condition

Osteoporosis is, in part, a natural consequence of ageing in postmenopausal women (Hodsman 2002). It is a skeletal disorder characterized by decreased bone mass and deterioration of the microarchitecture of bone, resulting in an increased risk of fracture (NIH Consensus 2001). The most common consequences of osteoporosis are fractures of the hip, wrist, and vertebrae (Hodsman 2002). "Bone strength reflects the integration of two main features: bone density and bone quality" (Brown 2002). The clinical indicator of 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 (for example, a fall from a standing height or less) (Brown 2002).

The diagnosis of osteoporosis is determined by the bone mineral density (BMD) values of the lumbar spine and hip, preferably assessed by dual energy X-ray absorptiometry (DXA) (WHO 2004). The interpretation of BMD is based on the comparison of a person's BMD with the mean value for a young adult population. The 'T-score' is the number of standard deviations (SDs) above or below the mean BMD for normal young adults (Brown 2002), for which the World Health Organization (WHO) Study Group recognizes four diagnostic categories for women (WHO 1994), as follows.

- 'Normal': a value for BMD or bone mineral content (BMC) within 1 SD of the young adult reference mean.
- Low bone mass (osteopenia): a value for BMD or BMC more than 1 SD below the young adult mean but less than 2.5 SDs below this value.
- Osteoporosis: a value for BMD or BMC 2.5 SDs or more below the young adult mean.
- Severe osteoporosis (established osteoporosis): a value for BMD or BMC more than 2.5 SDs below the young adult mean in the presence of one or more fragility fractures.

Based on the WHO criteria for hip BMD, the prevalence of osteoporosis amongst women aged 50 years and older in nine industrialized countries in North America, Europe, Japan, and Australia ranged from 9% (UK) to 15% (France and Germany), and was increased with the inclusion of spinal BMD, to range from 16% (USA) to 38% (Japan) (Wade 2014a). In 27 countries of the European Union, there were 22.1 million women with osteoporosis in 2010, four times as many women with osteoporosis as there were men (Kanis 2013).

However, there are limitations to the WHO definition. The predictive value of BMD for fracture varies, depending on the site selected, the database used for comparison, and the technology employed. Furthermore, T-scores do not provide a good basis on which to establish comparable diagnostic thresholds between different sites of interest and different bone mass measurement techniques (Black 2001). The between-site and technique variability introduces the potential for misclassification and inappropriate treatment. Therefore, the presence of pre-existing osteoporotic fractures is considered an important risk factor for future fractures (Hodsman 2002). As estimated from the Canadian Multicentre Osteoporosis Study (CaMos) cohort, women with a prevalent fracture after age 40, compared to those without, had an increased risk of future fracture (relative risk (RR) 2.3, 95% confidence interval (CI) 1.9 to 2.7), after adjusting for both age and BMD (Langsetmo 2009).

Osteoporosis-related morbidity is associated with significant medical and social consequences (Brown 2002). The cumulative lifetime fracture risk for a 50-year-old woman with osteoporosis is stated to be as high as 60% (Cummings 1989). The major source of morbidity and mortality from osteoporosis is attributed to hip fractures. An estimated 50% of women who sustain a hip fracture do not return to their previous functional state and become dependent on others for their daily activities (Brown 2002). Worldwide, in the year 2000, it was estimated that 5.5 million women would experience fractures; the hip was the second-most prevalent fracture site. Specifically for women, the total disability-adjusted life-years (DALYs) lost was 1.53 million, accounting for 41.4% of the global burden of osteoporosis (Johnell 2006). Mortality associated with hip fractures is high in the first year after a fracture, with a standardized mortality ratio (SMR) of 1.9 (95% CI 1.2 to 2.7), which remains elevated for up to 15 years (Melton 2013). The age-adjusted relative risk of dying following a clinical vertebral fracture was also found to increase almost ninefold, with a relative risk of 8.64 (95% CI 4.45 to 16.74) (Cauley 2000). The mortality impact of non-hip, non-vertebral (NHNV) fractures at the population level was studied in the CaMos cohort. Investigators found that the mortality risk following NHNV fractures (followed up for a median time exceeding 14 years) increased (hazard ratio (HR) 1.27, 95% CI 1.08 to 1.48), but not to the same extent as that for hip fractures (HR 2.14, 95% CI 1.62 to 2.84) and vertebral fractures (HR 1.93, 95% CI 1.42 to 2.64) (Tran 2017a).

It is worth noting that the occurrence of fracture is not exclusive to postmenopausal women with osteoporosis. In a population-based random sample of 616 postmenopausal women aged 60 to 94 years, 73.1% of the fractures occurred in postmenopausal women without osteoporosis (56.5% with osteopenia, and 16.6% with normal BMD) (Pasco 2006). From a large cohort of postmenopausal women aged 65 years or older (8065 women), 54% of the 243 women sustaining a hip fracture during the five-year follow-up were non-osteoporotic at baseline (Wainwright 2005a). In a study involving 482 women with no prior history of vertebral fracture, Greenspan 2001 found that women deemed "non-osteoporotic" based on various WHO classification criteria had indeed experienced vertebral fractures. For instance, amongst women classified as having osteopenia and normal bone mineral density (BMD) according to spine BMD alone, total hip BMD alone, femoral neck BMD alone, and any central site BMD, 36%, 34.6%, 30.7%, and 30.7% respectively, had sustained such fractures. The prevention of fractures, therefore, is an important issue for postmenopausal women across the BMD spectrum, who are considered to have different risks in terms of BMD T-score and previous fracture history.

Description of the intervention

Prevention and treatment of osteoporosis can be complex, due to the multifactorial aetiology of the disorder. A range of pharmaceutical interventions with different mechanisms has been shown to be effective in reducing fracture risk in postmenopausal women with osteoporosis (Crandall 2014). However, most currently-available osteoporosis drugs are anti-resorptive agents that act to decrease bone turnover. Bisphosphonates, one class of anti-resorptive drugs, are stable analogues of naturally-occurring pyrophosphates, which inhibit bone resorption through their effects on osteoclast function. Bisphosphonates 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 (Brown 2002).

Etidronate is a first-generation, non-nitrogen-containing bisphosphonate that inhibits osteoclastic resorption and decreases bone turnover (Fleisch 1997). Etidronate was also the first bisphosphonate studied for the treatment of osteoporosis (Ioachimescu 2007). It was widely used in Europe and Canada from around 1999 to 2008, as it was inexpensive and highly tolerable compared with the new bisphosphonates (Ioachimescu 2007; Rosen 1997). In Canada, etidronate was recommended as an option for menopausal women who were intolerant of other oral bisphosphonate first-line therapies, such as alendronate and risedronate (Papaioannou 2010). However, etidronate's prominence in anti-osteoporotic care has waned. Concerns regarding osteomalacia, alongside a strong media campaign and more compelling evidence favouring alendronate, have led not only to the US Food and Drug Administration's removal of etidronate for this indication but also to a transition from an off-label use of etidronate to alendronate (Rosen 1997).

How the intervention might work

Etidronate is given orally on an intermittent or cyclical schedule: 200 mg or 400 mg daily for two weeks every 90 days, followed by calcium, to minimize any potential to inhibit bone mineralization and result in osteomalacia.

Cyclical etidronate was also included in coherence therapy, also known as ADFR therapy (repeated cycles of activation, depression, free, repeat) (Frost 1980) – an approach to treating osteoporosis that has fallen out of fashion/use. In ADFR therapy, osteoclasts are activated through agents such as phosphorus or parathyroid hormone. Subsequently, limited etidronate usage suppresses osteoclastic activity, with treatment intervals allowing normal osteoblastic function before the cycle's repetition. Theoretically, this ADFR regimen could lead to a pronounced imbalance of bone remodelling in favour of bone formation (Frost 1980).

Etidronate has been shown to increase bone mineral density after one to three years of treatment, by 4.06% (95% CI 3.12 to 5.0) in the lumbar spine and 2.35% (95% CI 1.66 to 3.04) in the femoral neck (Cranney 2001). The anti-fracture effects of etidronate were investigated in a meta-analysis of 13 clinical trials (Cranney 2001). The meta-analysis indicated that etidronate reduced vertebral fractures by 37% (RR 0.63, 95% CI 0.44 to 0.92), but not those at other anatomic locations. Similar results were observed in the first version of this review (Wells 2008a), in which etidronate led to a better result for postmenopausal women with a higher risk of fracture than in those with a lower risk (secondary prevention: RR 0.53, 95% CI 0.32 to 0.87 versus primary prevention: RR 3.03, 95% CI 0.32 to 28.44). A prospective 7-year etidronate study indicated a trend towards lower rates of vertebral fractures with longer exposure: women receiving etidronate for two, four, five, or seven years had fracture rates of 152, 95, 52, and 12 per 1000 patient years, respectively. Etidronate also maintained its effects on bone mass for at least two years after therapy was stopped (Watts 1990, see Miller 1997 reference).

Why it is important to do this review

Although in recent years, etidronate has been considered a weaker anti-resorptive agent than the nitrogen-containing bisphosphonates (i.e. alendronate and risedronate) and is less widely used, it may remain an appealing alternative for osteoporotic care due to its ease of use (daily tablet for two weeks followed by 10 to 12 weeks without treatment), low cost, and safety profile (Ioachimescu 2007). Given the prevalence of menopausal osteoporosis and the increase in emerging therapies, an up-to-date and rigorously-conducted review which includes all available trials comparing etidronate to both placebo and active drugs will benefit current healthcare practice.

In this review update, we have added important outcomes that should be considered in anti-osteoporotic care, such as health-related quality of life, which considers etidronate's effects from women's perspectives. We have quantitatively analysed gastrointestinal adverse events, which have been linked to the use of oral bisphosphonates (Tadrous 2014), and accounted for a large proportion of adverse events and withdrawals from treatment in the previous version of this review (Wells 2008a). We added 'serious adverse events' as an outcome, along with rare adverse outcomes related to bisphosphonates, including osteonecrosis of the jaw (Lee 2014; Mavrokokki 2007), atypical femoral fracture (Edwards 2013; Khow 2017), and atrial fibrillation (Sharma 2014). We also investigated acute phase reaction, which has been linked to potent aminobisphosphonates (e.g. zoledronic acid and risedronate), including a rise in body temperature and flu-like symptoms (Hewitt 2005).

OBJECTIVES

To assess the benefits and harms of intermittent/cyclic etidronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women at lower and higher risk of fracture, respectively.

METHODS

Criteria for considering studies for this review

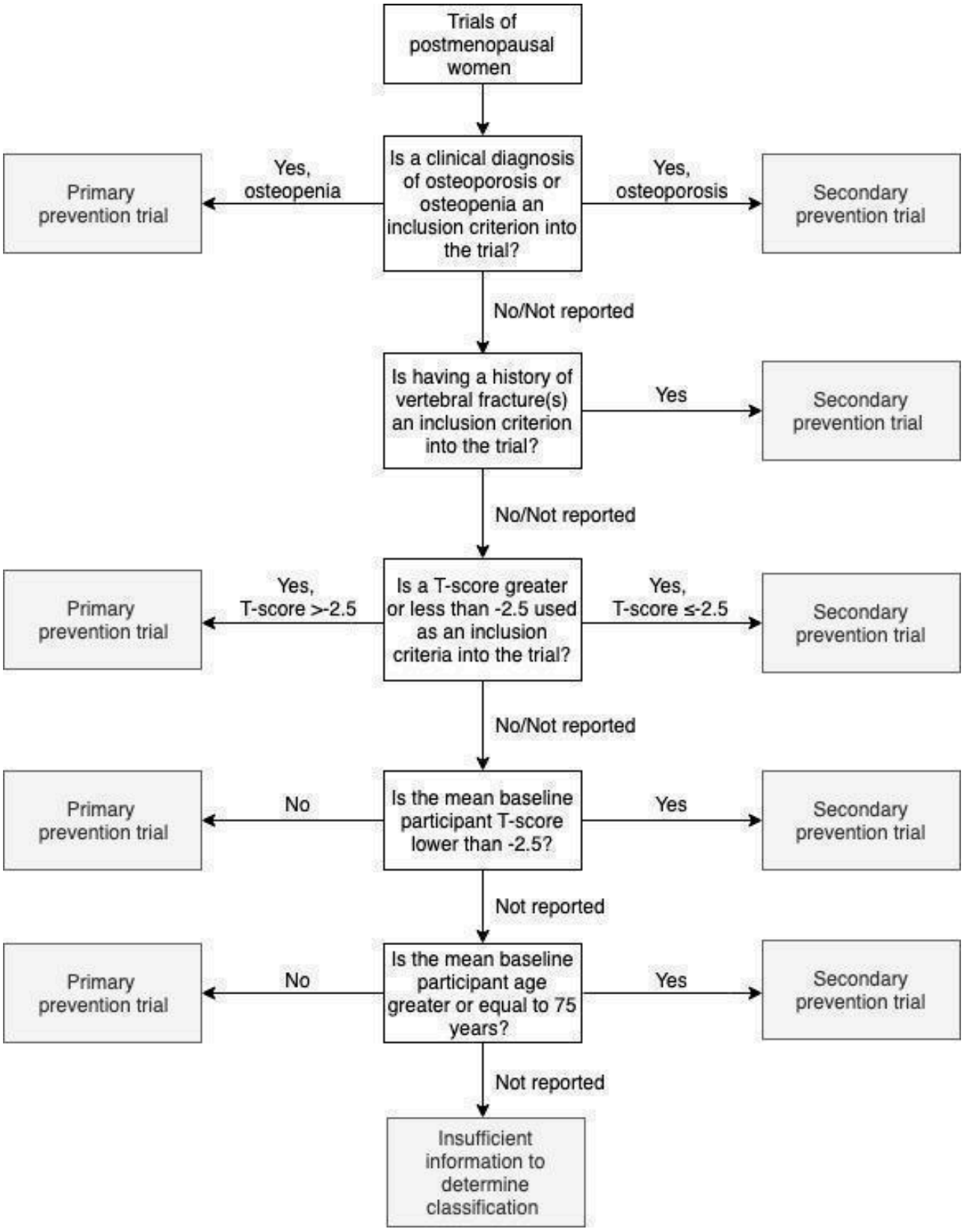
Types of studies

We included randomized controlled trials (RCTs) with a treatment duration of at least one year.

Types of participants

The population of interest included postmenopausal women with different risks of fracture. However, we excluded women with osteoporosis caused by an underlying disease or medication. Corresponding to the disease management in a clinical setting, we divided the population into primary prevention (participants who were at lower risk of osteoporotic fracture) and secondary prevention (participants who were at higher risk of osteoporotic fracture). To do this, we developed a hierarchical classification for primary and secondary prevention trials that gave more weight to study inclusion criteria than baseline statistics (Figure 1). We followed this hierarchy to classify trials as secondary prevention if the inclusion criteria of the trial fulfilled one of the following criteria:

Figure 1. Hierarchical classification algorithm for primary and secondary prevention trials



1. participants were diagnosed with osteoporosis;
2. participants were required to have a history of vertebral fractures;

3. participants' bone mineral density (BMD) was required to be at least 2.5 standard deviations (SD) lower than the bone density in young healthy adults (peak bone mass) BMD T-score, at any measured site (e.g. lumbar spine, hip, or other sites);
4. participants' mean baseline BMD T-score at any measured site was reported to be equal to or lower than -2.5;
5. participants were 75 years or older.

If none of the above criteria were met, we considered the study to be a primary prevention trial. The hierarchical classification was peer-reviewed and deemed to reflect current clinical guidelines and practices (NOGG 2017; WHO 1994; WHO 2004). We planned to conduct a sensitivity analysis excluding studies classified as secondary prevention trials based on the age criterion – a criterion that is less robust than the others in our hierarchy. If we could not classify studies using a hierarchical classification, we provided narrative descriptions instead.

Types of interventions

Treatment

Cyclic use of oral etidronate at 200 mg or 400 mg, or cyclic etidronate combined with another anti-osteoporotic drug.

Comparators

We included no treatment (e.g. placebo; calcium or vitamin D, or both) or any anti-osteoporotic drug for postmenopausal women. If the study used calcium or vitamin D controls or both, these same treatments would have to be given concurrently in the compared treatment groups. For studies using an ADFR regimen, the short-term concurrent use of an activator before the administration of etidronate or placebo was also regarded as a control treatment.

Types of outcome measures

Major outcomes

We considered fractures at the following anatomic sites, as well as two safety outcomes, as the most important review outcomes.

- Clinical vertebral fractures
- Non-vertebral fractures
- Hip fractures
- Wrist fractures
- Withdrawals due to adverse events
- Serious adverse events

Minor outcomes

- Radiographic or morphometric vertebral fractures
- Health-related quality of life
- Other safety outcomes related to bisphosphonate use, including gastrointestinal adverse events, acute phase reaction, osteonecrosis of the jaw, atypical femoral fracture, and atrial fibrillation.

Timing of outcome assessment

For all outcomes of interest, we extracted eligible measures at the longest time point (year) in the trial. However, for the fracture outcomes in subgroup analyses, we extracted data at multiple time points if such data were available.

Search methods for identification of studies

The electronic searches for this review were periodically updated in June 2012, August 2017, June 2019, March 2021, and February 2023. In the update search of June 2012, when the review scope was expanded to include randomized active-controlled trials of etidronate, we consulted the trial search coordinator in the Cochrane Musculoskeletal Group (CMSG) to broaden the search strategies, for which all the involved databases were searched from inception. In the following search updates, an experienced medical information specialist conducted the electronic searches with the same search strategies, extended to 26 August 2017, 5 June 2019, 26 March 2021, and 1 February 2023. We followed the Peer Review of Electronic Search Strategies (PRESS) 2015 guideline statement for systematic reviews to achieve comprehensiveness (McGowan 2016), whilst maintaining acceptable precision for the retrieved records.

A grey literature search was also conducted for each update.

Electronic searches

In the updated search on 1 February 2023, we searched the following databases, all on the Ovid platform: the Cochrane Central Register of Control Trials (CENTRAL), MEDLINE, Embase, and Evidence-Based Medicine Reviews. Search strategies used a combination of controlled vocabulary and keywords adjusted across databases, with no restrictions placed on language or date and form of publication. The full strategies from 2012, 2019, 2021, and the most recent (2023) search are in Appendix 1.

Searching other resources

We scrutinized the reference lists of all included studies and relevant systematic reviews and guidelines to identify any further relevant papers (Barrionuevo 2019; Chandran 2019; Ellis 2014; Hopkins 2011; Jansen 2011; Liu 2018; Migliore 2013; NOGG 2017; Taggart 2002; Yang 2016a; Zhou 2016). A grey literature search of ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) Search Portal was performed on 28 June 2019 to search for interventional studies involving etidronate. Studies retrieved from the clinical trial record databases were accessed at later dates for additional information. Drug approval documents and medical reviews developed by the US Food and Drug Administration, European Medicines Agency, and Health Canada were initially searched on 27 June 2019. No restrictions (on language, date, and form of publication) were applied to any of the searches. To avoid bias, we did not contact individual authors or organizations for further information.

Data collection and analysis

Selection of studies

Two review authors (of SH, CZ, JP, and WL) independently examined each title and abstract generated from the search and identified potentially eligible articles. We obtained the full-text articles for abstracts which were consistent with study eligibility. We only considered published studies for inclusion. Studies with eligible participants, interventions, and comparators were included, regardless of the reporting of outcomes of interest. We resolved any disagreement through discussion or, if required, consulted a third review author (GW or JP).

Data extraction and management

Double data entry was conducted by two review authors (of SH, CZ, WL, and JP), who independently abstracted data using standardized data abstraction forms created using web-based systematic review software (DistillerSR). We checked data accuracy, and resolved any discrepancies through discussion or, when required, by consulting a third review author (GW or SK). We also collected and checked information on pertinent methodological aspects of the study design and the characteristics of the participants.

Outcome data included definitions of the outcomes provided by the study authors, duration of treatment, and follow-up population (e.g. intention-to-treat, modified intention-to-treat, per-protocol, or safety population). For dichotomous outcomes, we recorded the number of people with events, follow-up participants included in the analysis, and total randomized participants. For health-related quality of life, we recorded the total number of randomized and follow-up participants, and the change from baseline if available. Fracture incidents were extracted from the reports of new occurrences of fractures independently measured at different skeletal sites (e.g. vertebral, non-vertebral, hip, and wrist); in other words, we tried to obtain the number of participants sustaining a fracture of interest. We defined vertebral fractures as clinical events or radiographic/morphometric events, according to the method of assessment. If the event was reported as an adverse event without any outcome definition, we classified it as a clinical vertebral fracture. However, for radiographic/morphometric events, there had to be a clear description of either radiographic or morphometric methods. In addition, all fracture outcomes were subject to subgroup analyses by treatment years. In other words, we tried to establish the yearly numbers of women sustaining the fracture of interest amongst the follow-up participants. If the follow-up yearly denominators were not available, we assumed a uniform dropout rate for each year and calculated the denominators by determining the proportion of participants 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 only reported end-of-study outcomes, we used these for our analysis, except for outcomes for which the numerator was zero for both comparison groups. In these instances, we included the outcome (with any necessary adjustments for follow-up denominators) for the earlier years of the study. For example, if a trial reported zero hip fractures for both treatment arms at the end of year three, we would also include in our analysis zero hip fractures for that trial at years one and two. We also inferred zero clinical vertebral, non-vertebral, hip, and wrist fractures if the study reported zero fractures of any kind. We documented any inferred data with reasons, which were agreed upon and consistent through the data extraction.

Our primary analyses – labelled 'base case analyses' in this review – distinguish primary and secondary prevention studies. They incorporate data available for the longest period (by year) for etidronate 400 mg/day or 200 mg/day in the placebo-controlled trials. The denominators used in our analyses are the numbers of women included in each study for a particular outcome.

For data reported in the extension of an original study, where either the study design changed or a large portion of the randomized participants were lost, we provided a narrative description in lieu of analysis.

Assessment of risk of bias in included studies

Two review authors (from SH, CZ, WL, SA, and AB) independently assessed the risks of bias (RoB) for each included study. Six methodological components recommended in the Cochrane review process were adopted and modified, as follows (Higgins 2017).

- Adequacy of sequence generation: whether the method with which the study generated the allocation sequence was sufficient to produce comparable groups in every aspect except for treatment.
- Allocation concealment: whether the concealment method adopted by the study was sufficient to prevent knowledge of the allocation sequence in advance of, or during, enrolment.
- Blinding: whether the measures, if applicable, were sufficient to blind study participants, personnel, and assessors from detecting which intervention a participant was receiving. Instead of assessing performance and detection bias in one core item, we divided it into the two following domains.
  - Performance bias for all outcomes: in clinical trials, to ensure that the effect estimates are a result of the intervention of interest and not biased by other factors (expected or unexpected), appropriate blinding methods to prevent the participants and personnel from knowing about the assigned treatment are required. In this review, the participants were required to take anti-osteoporotic medications via different drug delivery routes and dose schedules for at least one year. Their compliance and health behaviours could be influenced if blinding was not maintained throughout the study. For study personnel, effective blinding would ensure that they provided a similar amount of attention and ancillary treatment to the participants, regardless of group assignment.
  - We assessed detection bias for subjective and objective outcomes separately. Objective outcomes included all fracture incidents, which required clinical evidence or radiographic/morphometric assessment to make a diagnosis; these were thus less likely to be influenced by the lack of blinding or inappropriate blinding. Subjective outcomes included adverse events and health-related quality of life, for which the lack of blinding or inappropriate blinding could influence the participants' reporting and the assessors' knowledge of the allocated interventions, and give rise to detection bias. For objective outcomes, the diagnostic investigation would most likely be at low risk of bias, and for subjective outcomes (adverse events), vigilance and reporting behaviours of both patients and personnel could be influenced.
- Incomplete outcome data: we separated the assessment for attrition bias into two outcome groups – efficacy and safety – given that these are normally assessed using different statistical strategies. We expected studies which treated fractures as efficacy outcomes to use different statistical management methods (i.e. sample size calculation and approach to handling missing data) than studies which monitored fractures as adverse events. We took into consideration the completeness of outcome data (including attrition and exclusions from the analysis), the number of participants in each intervention group included in the analysis compared with the number randomized, reasons for the attrition/exclusions, and approaches to handling missing data. We arbitrarily took the overall completion rate

of 80% as a cutoff for low risk of bias. If it was close to 80%, we considered two more factors: (a) whether the numbers lost and the reasons for early discontinuations were balanced across treatment groups; and (b) if there was an adequate approach to handling missing data (i.e. imputation versus last observation carried forward (LOCF)).

- Selective reporting bias: in addition to the literature search, we searched ClinicalTrials.gov (https://clinicaltrials.gov/) and the World Health Organization's International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform) for the protocols of included studies. If the study protocol was available, we compared the prespecified outcomes with the reported outcomes in the published study. However, for those studies without accessible protocols, we compared the predefined outcomes of interest in the methods section of the published study with those reported in the results section of the published study.
- Other sources of bias: we assessed any concern outside the above domains that might have threatened the validity of the study, such as potential threats related to study designs (i.e. cross-over trials, early termination of a study, or single arm without clear explanations).

We provided a two-part description for each domain: the first part described what happened in the study, and the second part provided a risk of bias judgement, indicating a 'low', 'high', or 'unclear' (when there was insufficient information) risk. We resolved any disagreements in judgement through discussion amongst the authors until consensus was reached, or by asking a third review author to adjudicate. Where the detection and attrition risk of bias domains were not applicable to some studies – for example, because the study did not assess any of the review's objectively- or subjectively-assessed outcomes of interest – we did not assign a risk of judgement rating in those domains (and this is indicated by a white space in the "risk of bias summary" figure).

Measures of treatment effect

Most outcomes of interest in this review were dichotomous. We used relative risk (or risk ratio, RR) to estimate the treatment effects for clinical vertebral, non-vertebral, hip, and wrist fractures, withdrawals due to adverse events, serious adverse events, radiographic vertebral fractures, gastrointestinal adverse events, atypical femoral fractures, acute phase reaction, osteonecrosis of the jaw, and atrial fibrillation. For the only continuous outcome, health-related quality of life, we used mean differences between the two groups' change from baseline. To accommodate different measurement scales, we used the standardized mean difference (Deeks 2022). For both types of outcome data, we used the 95% confidence interval (CI) for the effect size to describe the uncertainty inherent in the point estimates. In the base case analyses, for comparisons that included studies reporting zero events for both treatment and control, we calculated the Peto odds ratio (POR), in addition to the RR. If both effect measures provided similar results, we presented the RR due to its superiority in interpreting comparative effectiveness and safety (Brockhaus 2014; Deeks 2022).

For all measures of treatment effect, we analysed and presented the evidence for primary and secondary prevention studies separately.

Unit of analysis issues

Most of our outcomes of interest were dichotomous, for which the unit of analysis was the number of participants experiencing the outcome amongst the number of participants followed up (denominators). Outcomes reported as number of events were not usable unless there were zero events or only one event, in which case zero or one participant could be inferred.

We did not limit studies to a parallel-group design. For cross-over trials meeting the inclusion criteria, we extracted data from the first study period only.

For all studies, we considered the longest follow-up with available data (by year) in the base case analyses. We scrutinized pair-wise comparisons extracted from studies comparing more than two intervention groups, to avoid double-counting of participants in the same meta-analysis (Deeks 2022).

Dealing with missing data

We did not contact the original researchers of included studies for missing data. However, we used the most complete data available and conducted sensitivity analyses to assess the robustness of the results when needed. When the end-of-study denominators were not available, we subtracted the total withdrawals from the baseline denominators in the respective groups to calculate the follow-up denominators. However, if the total withdrawals were not known, we then used baseline denominators.

When necessary, we plotted numbers/percentages of the events which were reported in figures with the web-based tool, WebPlotDigitizer-4.1 (Rohatgi 2019). Where we inferred, plotted, or calculated study data, we documented the relevant source and the review authors' reasoning.

Assessment of heterogeneity

When a meta-analysis was feasible, we presented the results in forest plots, and used the I^2 statistic to measure the percentage of variability in treatment effects due to between-study heterogeneity rather than chance. For any I^2 statistics greater than 50%, which may indicate substantial or considerable heterogeneity, we conducted a qualitative investigation of clinical and methodological differences across the included studies. We also tested for homogeneity using a Chi^2 test with a cutoff of $P = 0.10$ for the presence of statistical heterogeneity (Deeks 2022).

Assessment of reporting biases

We made efforts to link related references to the included studies and to avoid multiple uses of data that originated from the same study. When companion publications provided additional outcome data for a study, we listed those publications under the main study reference. When companion publications did not provide any additional outcome data, we collated and annotated those records with the reason 'Companion record to included study but with no additional outcome data'.

To assess reporting bias, we planned to test the funnel plot asymmetry (the effect estimates plotted against the standard error of the effect estimate) when there were 10 or more studies available for meta-analysis of a specific outcome. However, there were no meta-analyses with 10 or more studies in this review update.

In this review, we placed no restrictions on language, status of publication (e.g. conference abstracts), or the lack of an outcome of interest.

Data synthesis

In this review, we analysed and presented the evidence for primary and secondary prevention studies separately.

For dichotomous outcomes, we calculated the relative risk (RR) of fracture using a fixed-effect model, given that the participants included in the primary and secondary prevention studies were expected to be homogeneous. In addition, the findings of our original review (Wells 2008a), in which few studies were included and the event frequencies of outcomes of interest were low, indicated that the use of a fixed-effect model might provide a better estimate (Deeks 2022). However, an investigation of the extent of heterogeneity was provided with a non-significant test (P value > 0.10) (Deeks 2022). We calculated the pooled or weighted RRs using the Mantel-Haenszel method. For the pooled results, we calculated site-specific 95% confidence intervals (CIs) and tested for association using a Chi^2 test procedure with a P value of less than 0.05 for the presence of a statistical association. For continuous outcomes (e.g. health-related quality of life), we converted measures to a standardized mean difference and provided a pooled estimate with a 95% CI. We further assessed the precision of the estimates based on the likelihood that one would make a different decision if the true effect was near one end or the other of the 95% CI. If the range of the 95% CI indicated a failure to reject the null hypothesis of no difference between treatments, little or no effect of etidronate compared with the comparator was considered. Whenever a meta-analysis was not possible, we provided a descriptive summary.

For the base case analyses of the placebo-controlled trials, we followed our original review and defined a greater than 15% relative change with precision as being clinically important (Wells 2008a). For any observed important benefit, we calculated and presented the absolute risk reduction (ARR) and the number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH), to make the results more interpretable and applicable to clinical practice. For these calculations, the five-year risk of fracture in the untreated population was based on the FRACTURE Index (FI) (Appendix 2, Black 2001), and the lifetime and five-year age-specific risks in the untreated population were based on the model by Doherty 2001 (Appendix 3), for predicting osteoporotic fractures in postmenopausal women.

Subgroup analysis and investigation of heterogeneity

Given that the anti-fracture effects of etidronate might vary by different lengths of treatment, we conducted subgroup analyses estimating effect sizes for etidronate in fracture prevention at one, two, and three years, as well as at the end of the longest treatment period.

Furthermore, we suspected that women with prior bisphosphonate use may differ in treatment response from those who were bisphosphonate-naïve. Based on the primary studies' inclusion/exclusion criteria and participants' baseline characteristics, we targeted studies which exclusively included either bisphosphonate-experienced or -naïve participants, and compared the anti-fracture effects of etidronate amongst these exposure groups.

We conducted a qualitative investigation comparing the clinical and methodological differences across included studies for any meta-analysis in which we observed substantial or considerable heterogeneity (e.g. I^2 > than 50% and a non-significant test for heterogeneity with a P value < 0.1). If we found no explanation for the heterogeneity, particularly if there was inconsistency in the direction of effect, we presented the individual risks of the intervention and comparator instead of a pooled estimate.

Sensitivity analysis

To address the uncertainty regarding the effects of etidronate in relation to the assumptions made in the base case meta-analyses, we conducted the following sensitivity analyses:

- analyses including all randomized participants (baseline denominators) instead of follow-up participants. Although an intention-to-treat (ITT) analysis is often recommended as the least biased way to estimate intervention effects in randomized trials (Newell 1992a), it would likely underestimate the incidence of adverse health outcomes, such as fractures. This bias would be even more exaggerated in the trials where end-of-study data were extracted from a smaller population than all randomized participants (e.g. those with radiographs available for assessment for vertebral fractures). Two approaches to extracting the denominators for the study groups are therefore necessary to test the robustness of the results.
- studies with fracture as an efficacy outcome. Ideally, evaluating fractures as efficacy outcomes would provide better operational fracture definitions, allow for more thorough statistical methods, and would obtain sufficient power (sample size). However, when fractures are planned as safety outcomes, there is often a reliance on spontaneous adverse event reporting and the results are narratively described. Therefore, studies identifying fractures as an efficacy outcome could possibly present anti-fracture estimates closer to the truth. This assumption, nevertheless, needs further investigation.
- studies of high methodological quality, defined as full publication of peer-reviewed randomized studies (i.e. not conference abstracts) with low risk of bias for both allocation concealment (i.e. clearly reported methods used to conceal participant allocation) and incomplete outcome data (i.e. an end-of-treatment follow-up rate of at least 80% or close to 80% with balanced attrition numbers and reasons across treatment arms). We assumed that the results from studies with high methodological quality would be closer to the truth.
- analysis excluding primary/secondary prevention studies classified on age alone.
- analysis excluding studies applying an ADFR regimen.

Summary of findings and assessment of the certainty of the evidence

We constructed two summary of findings (SoF) tables, using the GRADE approach (GRADEpro GDT; Schünemann 2022a; Schünemann 2022b), to provide recommendations incorporating relevance, applicability, and certainty of evidence from this review (Santesso 2020). We presented the major outcome results for intermittent/cyclic etidronate 400 mg/day compared with placebo for primary and secondary prevention in these SoF tables, including four fracture outcomes (clinical vertebral, non-vertebral, hip, and wrist fractures) and two safety outcomes (withdrawals due to

adverse events and serious adverse events). We assessed the evidence for factors that reduce its certainty, including study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. Specifically, for imprecision, we considered both the optimal information size (OIS) and review information size (RIS). If the 95% CI included no effect, or a small effect less than clinically important (< 15% relative change), or both, we downgraded the evidence for imprecision, even if the OIS criterion was met (Schünemann 2022b).

For baseline fracture risk at different anatomic locations, we also applied the five-year risks of vertebral, non-vertebral, and hip fractures derived from the FRACTURE index (Black 2001), in addition to those estimated from the study population receiving placebo. For primary prevention, where the women were at lower risk of fractures, the assumed low and moderate fracture risks were derived from the FRACTURE index quintiles 1-2 and 5, respectively. For secondary prevention, where the women were at higher risk of fractures, assumed moderate to high fracture risks were derived from the FRACTURE index quintiles 5 and 8-13, respectively (Table 2, Appendix 2). Where the data were available, the anticipated absolute effects were shown for each clinical scenario.

In presenting the results, we took the certainty of the supporting evidence into account. We used terms such as 'increase', 'decrease', or 'no difference' when the certainty of the evidence was high, and the terms 'probably', 'may', and 'don't know/uncertain' when the certainty of the evidence was moderate, low, or very low, respectively (Santesso 2020; Schünemann 2022a).

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

For this review update, we conducted five systematic searches between 2012 and February 2023. These searches yielded a total of 2186 records (1835 records from database searches; 351 records from grey literature searches, including bibliographies and clinical trial registers). After removing duplicates, we screened the titles or abstracts of 1485 records and discarded 1389 as clearly irrelevant to the review. We retrieved the remaining 96 records in full text to examine these articles and abstracts further. Of these, we identified eight new studies (eight references) eligible for inclusion in the review, and excluded the remaining 88 articles. We excluded 12 studies with reasons (see Excluded studies for further details), and listed five studies (five references) as 'awaiting classification'.

The remaining 22 studies included in this review update were originally identified in the first version of this review (Wells 2008a). The 11 studies included in the 2008 review were also included in this review update (Herd 1997; Ishida 2004; Lyritis 1997; Meunier 1997; Montessori 1997; Pacifici 1988; Pouilles 1997; Shiota 2001; Storm 1990; Watts 1990; Wimalawansa 1998). The 2008 review restricted inclusion to studies comparing etidronate to placebo/no treatment. For this update, we decided that studies comparing either two different doses of etidronate or comparing etidronate to another anti-osteoporotic agent were eligible for inclusion. We also decided to include studies that did not assess any of the review's fracture outcomes, if they were otherwise eligible. This expanded scope meant that 11 studies that were excluded in Wells 2008a were reclassified as included studies in this update (see further details in Included studies).

See Figure 2 for a flow diagram of the search results.

Figure 2. Study flow diagram

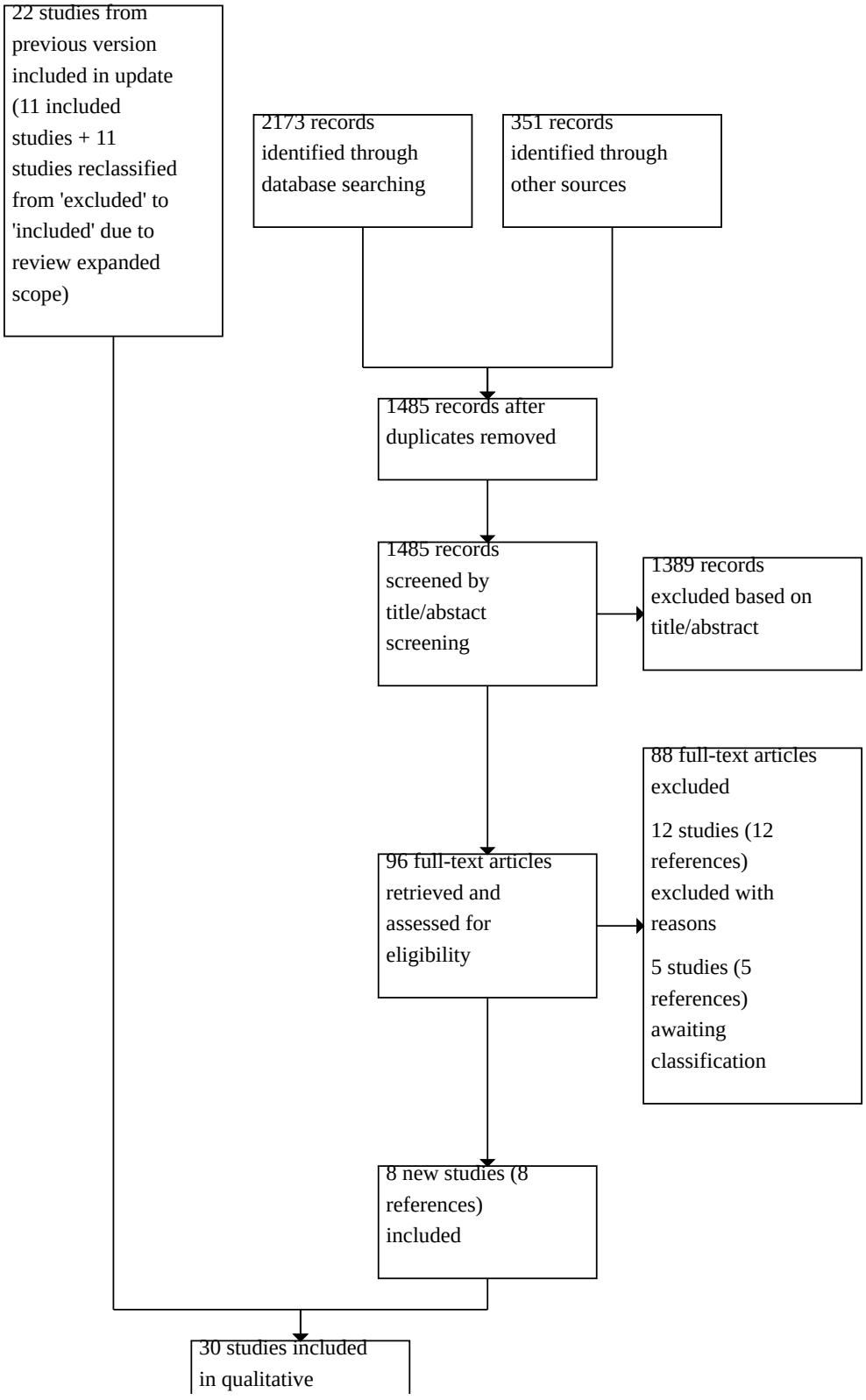
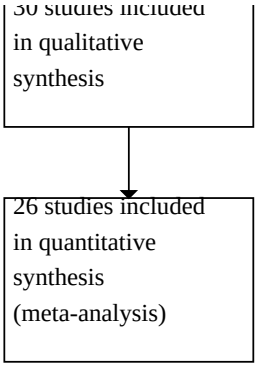


Figure 2. (Continued)



Included studies

As noted above, in this updated review, we included 30 randomized trials that reported at least one outcome of interest. In addition to the 11 studies included in the previous review (Herd 1997; Ishida 2004; Lyritis 1997; Meunier 1997; Montessori 1997; Pacifici 1988; Pouilles 1997; Shiota 2001; Storm 1990; Watts 1990; Wimalawansa 1998), we included six studies previously excluded for lacking fracture outcomes (Adami 2000; Chilibeck 2002; Evans 1993; Gürlek 1997; Heath 2000; Wimalawansa 1995), and another five with active comparator groups (Guañabens 2000; Iwamoto 2001; Iwamoto 2003b; Masud 1998; Steiniche 1991), reflecting the expanded scope of this update compared to the Wells 2008a version. Additionally, eight new studies were included (Fukunaga 2002; Hasling 1994; Hu 2005; Iwamoto 2005; Köşüş 2005; Russo 1996; Sahota 2000; Tobias 1997). All trials were parallel-group studies. Details of the studies and the risk of bias assessments are provided in the Characteristics of included studies table.

Using our hierarchy (see Types of participants), we classified 10 studies as primary prevention and 20 as secondary prevention studies. Table 1 summarizes the criteria used to classify the included studies into primary and secondary prevention populations. Most studies met more than one classification criterion. However, we defined three studies as primary prevention based on the age criterion alone (Evans 1993; Montessori 1997; Pouilles 1997). We were unable to include four studies (one primary (Evans 1993) and three secondary prevention (Hasling 1994; Hu 2005; Pacifici 1988)) in the quantitative synthesis, as their outcome data were not extractable/usable. Instead, we describe these studies narratively in Appendix 4.

We included the remaining 26 studies in the quantitative analysis, with nine defined as primary prevention (Adami 2000; Chilibeck 2002; Heath 2000; Herd 1997; Meunier 1997; Montessori 1997; Pouilles 1997; Tobias 1997; Wimalawansa 1995), and 17 as secondary prevention (Fukunaga 2002; Guañabens 2000; Gürlek 1997; Ishida 2004; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Lyritis 1997; Masud 1998; Russo 1996; Sahota 2000; Shiota 2001; Steiniche 1991; Storm 1990; Watts 1990; Wimalawansa 1998). They were all randomized controlled trials published between 1990 and 2005. Except for one study which did not report the location (Wimalawansa 1998), all the studies were conducted in a single country. Etidronate was the subject of fewer studies after the late 1990s when newer bisphosphonates and anti-osteoporotic medications became available. Five of the six trials published after 2000 were conducted in Japan, recruiting Asian women (Fukunaga 2002; Ishida 2004; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Shiota 2001). In the remaining ten studies for which information regarding participants' ethnicity/race was available, 98% of the women were white (Adami 2000; Chilibeck 2002; Gürlek 1997; Herd 1997; Masud 1998; Meunier 1997; Montessori 1997; Pouilles 1997; Wimalawansa 1995; Wimalawansa 1998). Five trials were conducted in more than one centre (Adami 2000; Fukunaga 2002; Guañabens 2000; Pouilles 1997; Watts 1990). Ten studies (37%) reported their sources of funding, as follows: one (4%) was not funded (Iwamoto 2005); two (7%) were funded by not-for-profit organizations (Chilibeck 2002; Masud 1998); and seven (26%) were founded by industry (Fukunaga 2002; Meunier 1997; Montessori 1997; Sahota 2000; Steiniche 1991; Storm 1990; Watts 1990). Seventeen (63%), four (15%), four (15%), and one (4%) trial had two, three, four, and six arms, respectively. Whereas all the primary versus 35% of the secondary prevention studies reported pairwise comparison data for etidronate versus placebo or no treatment, a higher portion of secondary prevention studies provided comparisons of etidronate (alone or combined with other active agents) versus other osteoporotic drugs/combinations (primary: one study (11%) versus secondary: 13 studies (76%)).

As recommended, the included studies used etidronate in a 14-day intermittent and cyclic regimen, except for Lyritis 1997, in which a 20-day cycle was adopted. The off-treatment (for etidronate or the comparator) durations varied, as follows: 60 days (one study, Gürlek 1997), 70 days (six studies, Fukunaga 2002; Ishida 2004; Lyritis 1997; Shiota 2001; Wimalawansa 1995; Wimalawansa 1998), 76 days (14 studies, Adami 2000; Chilibeck 2002; Guañabens 2000; Heath 2000; Herd 1997; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Masud 1998; Montessori 1997; Russo 1996; Sahota 2000; Tobias 1997), 77 days (three studies, Meunier 1997; Pouilles 1997; Watts 1990), and 91 days (two studies, Steiniche 1991; Storm 1990). The concurrent use of calcium and/or vitamin D also varied. In Ishida 2004, no supplementation was provided. Eight trials provided continuous calcium and/or vitamin D to all participants (Chilibeck 2002; Fukunaga 2002; Gürlek 1997; Iwamoto 2003b; Lyritis 1997; Steiniche 1991; Storm 1990; Wimalawansa 1998), whilst in 15 trials, the background supplements were not given to participants during the periods in which they were receiving etidronate (Adami 2000; Guañabens 2000; Heath 2000; Herd 1997; Köşüş 2005; Masud 1998; Meunier 1997; Montessori

1997; Pouilles 1997; Russo 1996; Sahota 2000; Shiota 2001; Tobias 1997; Watts 1990; Wimalawansa 1995). The daily dose of concurrent calcium ranged from 100 mg to 1000 mg and vitamin D was provided at 400 IU. One study, Shiota 2001, used the derivative of vitamin D, alfacalcidol (0.5 µg/day), while two studies encouraged participants to consume dietary calcium and/or vitamin D instead of supplements (Iwamoto 2001; Iwamoto 2005). It is worth noting that two Japanese studies investigating etidronate incorporated an ADFR regimen, with the use of different activators: 1,25-dihydroxyvitamin D_3 (2 µg/day) for five days (Lyritis 1997), and phosphate 1 g twice a day for three days (Watts 1990).

The included sample size ranged from 30 (Gürlek 1997) to 429 (Watts 1990), with a median of 72 (Iwamoto 2001; Wimalawansa 1998). Only three primary prevention (Adami 2000; Herd 1997; Pouilles 1997) and six secondary prevention studies (Fukunaga 2002; Guañabens 2000; Ishida 2004; Lyritis 1997; Sahota 2000; Watts 1990) randomized more than 100 women into the trial. The completion rates ranged from 61% (Storm 1990) to 100% (Gürlek 1997; Iwamoto 2003b; Iwamoto 2005). All studies lasted longer than one year, amongst which eight, 10, three, three, and two had a duration of one, two, three, four, and five years, respectively. In total, 2770 women were included in the quantitative analyses.

As expected, participants (n = 740) in the primary prevention studies had fewer (or milder) risk factors than participants (n = 2030) in the secondary prevention trials, as follows.

- Age: primary: 49 to 63 years old (median 53) versus secondary: 50 to 72 years old (median 65)
- Time since menopause: primary: two to 15 years (median three) versus secondary: five to 26 years (median 18)
- BMD T-score at femoral neck: primary: 0.78 to -0.95 (median -0.08) versus secondary: -2.8 (which was only reported by one study (Guañabens 2000); or at lumbar spine: primary: -1.04 to -1.14 (median -1.09) versus secondary: -2.97 to -3.30 (median -3.14)
- Prevalent vertebral fractures: primary: 0% to 35% (median 0%) versus secondary: 0% to 100% (median 100%)

However, participants included in the primary prevention studies had higher body mass index scores than those included in the secondary prevention studies: primary: 24.4 to 27.0 kg/m^2 (median 25.7) versus secondary: 20.9 to 26.9 kg/m^2 (median 24.8). Regarding prior osteoporotic treatment, none of the primary or secondary studies exclusively recruited participants who had previous exposure to any bisphosphonate. However, four (44%) primary prevention (Adami 2000; Herd 1997; Meunier 1997; Wimalawansa 1995) and 11 (65%) secondary prevention studies (Guañabens 2000; Gürlek 1997; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Masud 1998; Russo 1996; Sahota 2000; Storm 1990; Watts 1990; Wimalawansa 1998) included only bisphosphonate-naïve participants.

Excluded studies

Twelve studies that initially appeared to meet the inclusion criteria are documented, along with the reasons for their exclusion (Higgins 2022; Lefebvre 2022), as follows:

- ineligible population: one study excluded in the 2008 version of the review remained excluded (Miller 1999), and five studies were newly excluded in this update (Fujita 1993; Fujita 2009; Kushida 2004; Pearson 1997; Yamaguchi 2005);
- ineligible intervention: one study remained excluded (Iwamoto 2002), and three studies were newly excluded in this update (Caffarelli 2010; Struijs 1996; Zhu 2004);
- insufficient treatment duration (on-treatment duration < one year): both studies were excluded in the previous version of the review (Heaney 1976; Iwamoto 2003a).

See Characteristics of excluded studies for details.

Studies awaiting classification

In an update search in 2021, we identified only one registered protocol (JapicCTI-050093), which included an unknown percentage of men and did not report any outcome of interest. We listed this protocol as 'awaiting classification', together with four other studies not reporting any outcomes of interest. We made no modifications to the existing body of evidence. See Characteristics of studies awaiting classificationfor details.

Risk of bias in included studies

We assessed the risk of bias of all 30 studies included in the qualitative synthesis (see Characteristics of included studies for details). Here we present a summary of the risk of bias assessments only for the 26 studies included in the quantitative synthesis.

Allocation

Sequence generation

Only seven (27%) of 26 studies clearly described methods for sequence generation that we judged to be appropriate, including the use of a computerized randomization schedule or code (Gürlek 1997; Montessori 1997; Shiota 2001; Storm 1990; Watts 1990; Wimalawansa 1998) or minimisation (Ishida 2004). In one study (4%), Iwamoto 2005, the participants were divided "one by one in the order of recruiting", which we considered inadequate and subject to high risk of bias. The remaining 18 studies (69%) used descriptors such as "randomized", "randomly assigned", "randomly divided", or "randomization scheme" but did not provide sufficient information to permit a judgement of low or high risk.

Allocation concealment

None of the included studies reported an acceptable approach to concealing the allocation list, or confirmed that the randomization schedule remained unknown throughout the study, or both. We judged 25 studies (96%) which did not provide a description of (appropriate) relevant methods to be at unclear risk of bias in this domain. We judged the Iwamoto 2005 study to be at high risk of bias in this domain because the stakeholders involved could have easily guessed the allocated treatment with the sequence generation method (i.e. "one-by-one in the order of recruiting"), regardless of any allocation concealment method.

We judged that none of the studies were at low risk of bias for both sequence generation and allocation concealment. Therefore, none were found to effectively prevent selection bias.

Blinding

In this domain, we separated the assessment for performance bias (all outcomes) and detection bias (objective and subjective outcomes).

Performance bias (all outcomes)

Appropriate blinding to avoid performance bias must effectively prevent the participants and personnel from knowing the assigned treatment. In this review, only Meunier 1997 used an "identical" placebo, and Fukunaga 2002 confirmed that the placebo was indistinguishable from the study drug in terms of smell, taste, and shape, which supported their claim of having a double-blind design. We judged these two studies (8%) to be at low risk of performance bias. We judged seven studies (27%) to be at unclear risk of performance bias, all of which claimed to be double-blind design but did not provide any supporting information (Adami 2000; Chilibeck 2002; Herd 1997; Pouilles 1997; Storm 1990; Tobias 1997; Watts 1990). We judged 17 studies (65%) to be at high risk of bias in this domain: this included eight studies which did not mention blinding at all and gave participants treatments that appeared distinguishable (Guañabens 2000; Gürlek 1997; Ishida 2004; Montessori 1997; Russo 1996; Steiniche 1991; Wimalawansa 1995; Wimalawansa 1998), and nine open-label studies (Heath 2000; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Lyritis 1997; Masud 1998; Sahota 2000; Shiota 2001).

Detection bias (objective outcomes)

For objective outcomes, we judged all 16 studies reporting any fracture data for analysis to be at low risk of bias regardless of the blinding methods used (Fukunaga 2002; Guañabens 2000; Herd 1997; Ishida 2004; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Lyritis 1997; Meunier 1997; Montessori 1997; Pouilles 1997; Russo 1996; Shiota 2001; Storm 1990; Watts 1990; Wimalawansa 1998). The assessment of this domain was not applicable to 10 studies, as they did not provide any usable fracture data (Adami 2000; Chilibeck 2002; Gürlek 1997; Heath 2000; Köşüş 2005; Masud 1998; Sahota 2000; Steiniche 1991; Tobias 1997; Wimalawansa 1995).

Detection bias (subjective outcomes)

For subjective outcomes that mainly rely on the participants' reporting of adverse events and the outcome assessor's judgement, it is essential to have effective blinding methods to prevent them from knowing the assigned treatment. For this domain, 25 of 26 studies reported at least one usable subjective outcome. Two double-blind studies also provided appropriate blinding methods (8%, Fukunaga 2002; Meunier 1997), which we considered to be effective in maintaining the blinding for participants who reported the adverse events and for outcome assessors (low risk). However, we judged 16 studies (64%) to have a high risk of detection bias due to: an open-label design (nine studies: Heath 2000; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Lyritis 1997; Masud 1998; Sahota 2000; Shiota 2001); or the absence of any mention of blinding in the face of interventions that would easily be differentiated (seven studies: Guañabens 2000; Gürlek 1997; Ishida 2004; Russo 1996; Steiniche 1991; Wimalawansa 1995; Wimalawansa 1998). We judged the remaining seven studies (28%) – which claimed to be double-blind or to use placebo – to be at unclear risk of detection bias due to the lack of information to support the effectiveness of the blinding (Adami 2000; Chilibeck 2002; Herd 1997; Pouilles 1997; Storm 1990; Tobias 1997; Watts 1990).

One study, Montessori 1997, did not report any subjective outcome of interest to allow for assessment.

Incomplete outcome data

Attrition bias (efficacy outcomes)

Sixteen of 26 studies reporting at least one usable efficacy outcome data were assessed. We judged nine studies (56%) as having a low risk of attrition bias, as they had adequate completion rates (ranging from 81% to 100%, median 85%), with balanced withdrawals and reasons for the early discontinuations across groups, or they provided an appropriate approach to handling missing data when needed, or both (Fukunaga 2002; Herd 1997; Ishida 2004; Iwamoto 2003b; Iwamoto 2005; Meunier 1997; Pouilles 1997; Watts 1990; Wimalawansa 1998). We assessed four studies as high risk in this domain, as they had comparatively low overall completion rates (ranging from 61% to 80%, median 70%), or imbalanced or unclear attrition information across groups, or both (Guañabens 2000; Lyritis 1997; Montessori 1997; Storm 1990). We judged the remaining three studies (19%) to be at unclear risk of bias, as they provided insufficient information for assessment (Iwamoto 2001; Russo 1996; Shiota 2001).

The remaining ten studies which did not report any efficacy outcome of interest were not assessed in this domain (Adami 2000; Chilibeck 2002; Gürlek 1997; Heath 2000; Köşüş 2005; Masud 1998; Sahota 2000; Steiniche 1991; Tobias 1997; Wimalawansa 1995).

Attrition bias (safety outcomes)

All 26 studies reported at least one safety outcome. The criteria for assessing risk from incomplete outcome data were the same as those for efficacy outcomes. We judged 15 studies (58%) to be at low risk of bias, 13 of which had a completion rate greater than 80% and balanced attrition and reasons for withdrawals across groups (Fukunaga 2002; Chilibeck 2002; Gürlek 1997; Herd 1997; Ishida 2004; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Masud 1998; Meunier 1997; Pouilles 1997; Sahota 2000; Wimalawansa 1998). The other two studies – which had unclear attrition information (Tobias 1997) or a low completion rate (78%, Wimalawansa 1995) – reported only withdrawals due to adverse events and included all randomized participants, so the estimates of the effect sizes were less likely biased. We judged six studies (23%) reporting safety outcomes to be at high risk of bias due to high attrition, unbalanced discontinuations across groups, or both (Adami 2000; Guañabens 2000; Heath 2000; Lyritis 1997; Montessori 1997; Storm 1990). We assessed the remaining five studies (19%) to have an unclear risk of bias in this domain due to insufficient attrition reporting (Iwamoto 2001; Russo 1996; Shiota 2001; Steiniche 1991; Watts 1990).

Selective reporting

We judged all but seven included studies (73%) reporting at least one outcome of interest to be at low risk of bias for selective reporting. We judged six studies (23%) to be at unclear risk of bias in this domain due to limited information: Köşüş 2005 was a brief report, and the results for Tobias 1997 were reported in a letter to the editor. Four studies did not appear to monitor or report any safety outcomes or adverse events, which does not meet the reporting standards for clinical trials (Chilibeck 2002; Ishida 2004; Masud 1998; Sahota 2000).

One study (4%), Storm 1990, did not report serious adverse events, but there were 10 withdrawals due to deaths (five in each group). It was unclear whether the study had overlooked other safety results, so we judged it to be at high risk of bias.

Other potential sources of bias

Of 26 studies, we considered 17 (65%) to be free of other sources of bias (low risk). We judged four studies (15%) to be at high risk of bias from other sources. The first author of three studies (Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005), was later found to be involved in a study retraction (Koziol 2017). Therefore, we judged all the trials led by this author to be potentially high risk, as well as one study (Ishida 2004), which was suspected to be fraudulent but was not retracted (Avenell 2020).

We judged five studies (19%) to be at unclear risk of bias. Chilibeck 2002 originally had a four-arm factorial study design: (1) exercise plus placebo; (2) no exercise plus placebo; (3) etidronate plus exercise; and (4) etidronate plus no exercise. For comparison purposes, we combined the first two arms as the placebo group and compared these to the latter two, as the etidronate group. The omission of the effectiveness of exercise might have introduced bias. We judged Köşüş 2005, Russo 1996, and Tobias 1997 to be at unclear risk of other bias since the information provided in their brief publications was insufficient for assessment. Montessori 1997 was originally a two-year trial, but at the end of the study, they decided to extend it for another year. The extension did not appear to be pre-planned and information about the amendment was not provided. The impact of the change on risk of bias is unclear.

Summary assessment of risk of bias

Figure 3 provides a graphical summary of risk of bias for the 30 included studies, and Figure 4 summarizes the percentages of included studies at low, unclear, or high risk of bias in each assessment domain.

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study (30 eligible studies).

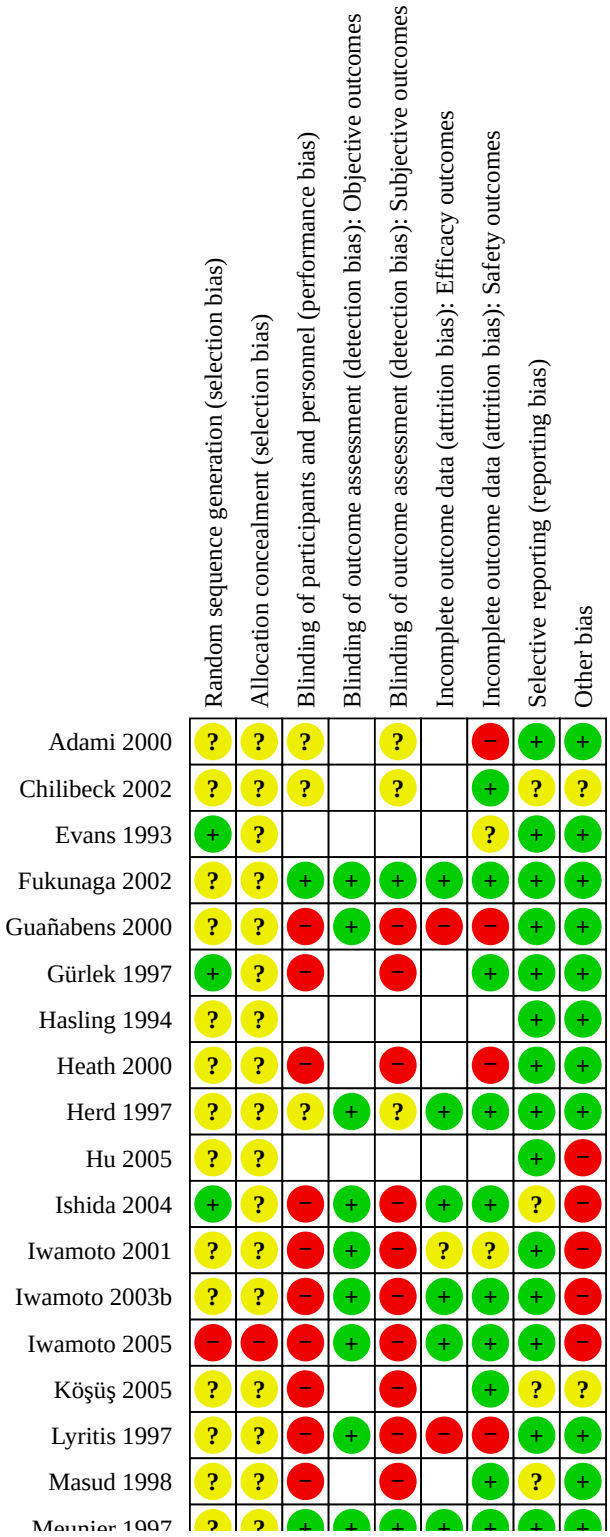


Figure 3. (Continued)

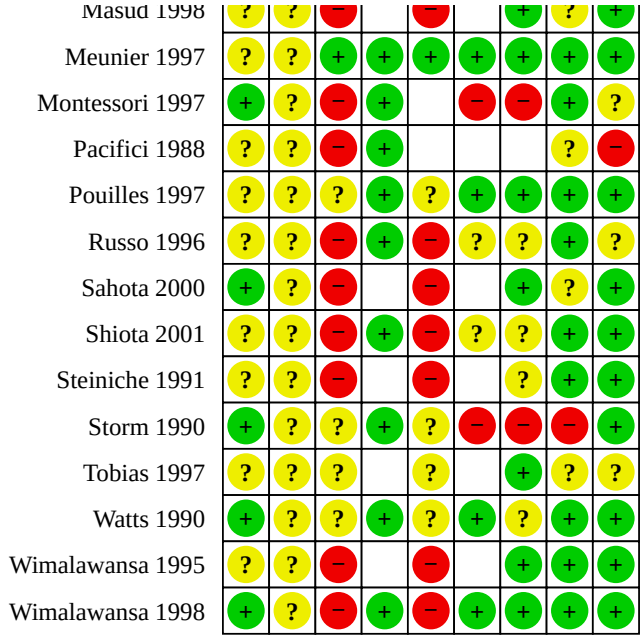
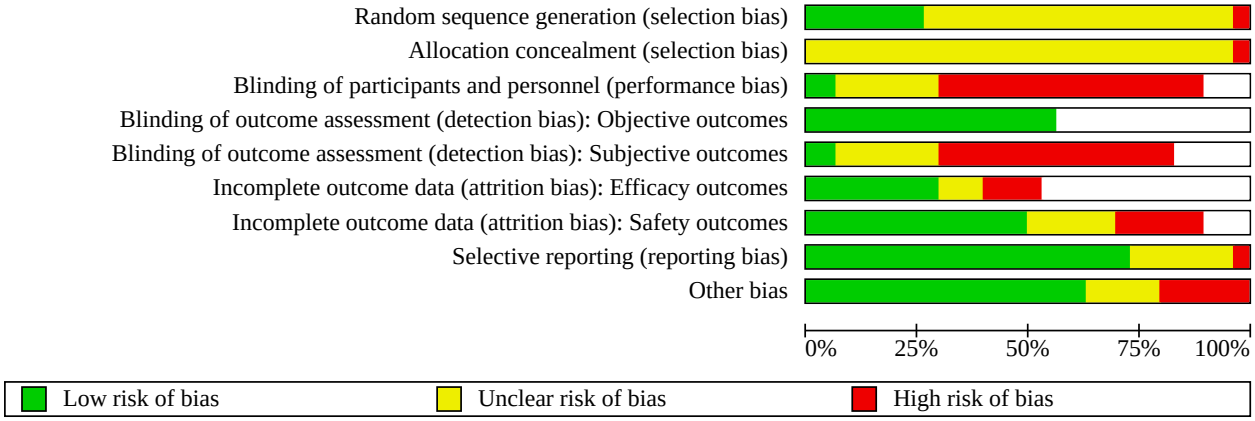


Figure 4. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies (30 eligible studies).



We judged none of the 26 studies included in the quantitative synthesis to be at low risk of bias for all seven domains. "Allocation concealment" was overlooked by all studies, with 96% (25/26) subject to unclear risk of bias for insufficient information and 4% (1/26) to high risk as a result of inadequate methods. For "sequence generation", only 27% (7/26) of the studies provided methods which were considered adequate, while 69% (18/26) and 4% (1/26) were marked down due to unclear information and inadequate methods, respectively. We judged none of the studies to be at low risk of bias in both "sequence generation" and "allocation concealment"; therefore, all were at risk for selection bias.

For performance bias, 8% (2/26) of the studies described methods that we judged were sufficient to prevent both participants and personnel from knowing which treatment had been assigned. We judged seven studies (27%) to be at unclear risk due to a lack of detail confirming the blinding. We assessed over half of the studies (65%, 17/26) as high risk because they were either described as open-label or blinding was not feasible within the study context. For detection bias, we assessed objective and subjective outcomes separately. For the former, we judged all 16 studies (100%) reporting at least one objective outcome to be at low risk of bias. For the latter, 25 of 26 studies reported at least one subjective outcome that we could assess. We judged 8% (2/25), 28% (7/25), and 64% (16/25) of these studies to be at low, unclear, and high risk of bias, respectively.

For attrition bias, we assessed 16 and 26 studies for efficacy and safety outcomes, respectively. We judged 56% (9/16) of the former and 58% (15/26) of the latter to be at low risk of bias.

The criteria for "selective reporting" and "other bias" domains were well fulfilled by 73% (19/26) and 65% (17/26) of the studies, respectively.

Effects of interventions

See: **Summary of findings 1** Intermittent/cyclic etidronate 400 mg/day compared to placebo for the primary prevention of osteoporotic fractures in postmenopausal women; **Summary of findings 2** Intermittent/cyclic etidronate 400 mg/day compared to placebo for the secondary prevention of osteoporotic fractures in postmenopausal women

Base case analyses

Comparison 1. Etidronate 400 mg/day versus placebo

For cyclic etidronate 400 mg/day compared with placebo, the base case analyses for the six major outcomes are presented in Analysis 1.1 to Analysis 1.4, Analysis 1.6, and Analysis 1.7, and the results are summarized in Table 2. In total, nine primary (740 participants) (Adami 2000; Chilibeck 2002; Heath 2000; Herd 1997; Meunier 1997; Montessori 1997; Pouilles 1997; Tobias 1997; Wimalawansa 1995) and four secondary prevention studies (667 participants) (Lyritis 1997; Storm 1990; Watts 1990; Wimalawansa 1998) reported data for at least one major outcome.

Major outcomes

Clinical vertebral fractures

For primary prevention, two studies reported data (Meunier 1997; Pouilles 1997). In total, two of 81 women receiving etidronate versus zero of 82 women receiving placebo sustained at least one clinical vertebral fracture. A pooled risk ratio (RR) of 3.03 (95% confidence interval (CI) 0.32 to 28.44), estimated from low-certainty evidence, indicated that etidronate may result in little to no difference in clinical vertebral fractures. See Analysis 1.1;Table 2.

None of the secondary prevention studies reported this outcome.

Non-vertebral fractures

For primary prevention, two studies collectively reported that five women receiving etidronate 400 mg/day and nine receiving placebo experienced an incident (Meunier 1997; Pouilles 1997). The pooled risks for etidronate and placebo were 6.2% and 11.1%, respectively; and the estimate of the RR was 0.56 (95% CI 0.20 to 1.61). The moderate-certainty evidence indicated that etidronate 400 mg/day probably resulted in little to no difference in non-vertebral fractures. See Analysis 1.2;Table 2.

For secondary prevention, four studies collectively reported that this outcome occurred in 43 of 312 women receiving etidronate and 40 of 312 receiving placebo (Lyritis 1997; Storm 1990; Watts 1990; Wimalawansa 1998). The low-certainty evidence indicated that etidronate may result in little to no difference in non-vertebral fractures (RR 1.07, 95% CI 0.72 to 1.58).

Hip fractures

Two primary prevention studies reported zero incidents amongst 94 and 95 women receiving etidronate and placebo, respectively (Meunier 1997; Pouilles 1997). Based on the limited evidence assessed as very low certainty, the effect size for this outcome was not estimable. The effects of etidronate 400 mg/day on hip fractures are not known (Analysis 1.3;Table 2).

Two secondary prevention studies reported data for hip fractures (Lyritis 1997; Watts 1990). In total, two women in each of the etidronate- and placebo-treated groups sustained a fracture. The evidence is very uncertain about the effect of etidronate on hip fracture (RR 0.93, 95% CI 0.17 to 5.19; very low-certainty evidence).

Wrist fractures

None of the primary prevention studies reported this outcome.

For secondary prevention, two studies reported data: Storm 1990 reported zero events and Lyritis 1997 reported two women in each of the etidronate and placebo groups experienced at least one incident. The evidence is very uncertain about the effect of etidronate on wrist fracture (RR 0.90, 95% CI 0.13 to 6.04; Peto odds ratio (POR) 0.89, 95% CI 0.12 to 6.63; very low-certainty evidence; Analysis 1.4; Table 2).

Withdrawals due to adverse events

Eight primary prevention studies reported this outcome (Adami 2000; Chilibeck 2002; Heath 2000; Herd 1997; Meunier 1997; Pouilles 1997; Tobias 1997; Wimalawansa 1995). In total, 8.4% of women (25/298) receiving etidronate versus 5.7% of those receiving placebo (17/299) discontinued the study early because of adverse events. Etidronate 400 mg/day may result in little to no difference in withdrawal due to adverse events compared to placebo (RR 1.41, 95% CI 0.81 to 2.47; low-certainty evidence; Analysis 1.6;Table 2).

For secondary prevention, four studies collectively reported that 14 of 312 women receiving etidronate and 13 of 312 women receiving placebo failed to complete the study due to adverse events (Lyritis 1997; Storm 1990; Watts 1990; Wimalawansa 1998). The evidence is very uncertain about the effect of etidronate on withdrawals due to adverse events (RR 1.09, 95% CI 0.54 to 2.18; POR 1.10, 95% CI 0.49 to 2.49; very low-certainty evidence).

Serious adverse events

Five primary prevention studies reported that at least one serious adverse occurred in 22 (8.9%) and 25 women (10.0%) in the etidronate and placebo groups, respectively (Adami 2000; Heath 2000; Herd 1997; Meunier 1997; Pouilles 1997). Based on moderate-certainty evidence, the estimated RR 0.90 (95% CI 0.52 to 1.54) demonstrated that etidronate 400 mg/day probably results in little to no difference in serious adverse events (Analysis 1.7;Table 2).

Only one secondary prevention study reported this outcome, in which zero incidents occurred, so the RR was inestimable (Lyritis 1997). We assessed the limited evidence as very low certainty; therefore, the effects of etidronate 400 mg/day on serious adverse events are not known.

Minor outcomes

Only three minor outcomes were reported for the 400 mg dose of etidronate. None of the studies for this comparison reported health-related quality of life, acute phase reaction, osteonecrosis of the jaw, or atrial fibrillation. Detailed comparisons are presented in Table 3.

Radiographic vertebral fractures

For primary prevention, two studies reported data. Herd 1997 reported zero radiographic vertebral fractures, while Montessori 1997 reported that zero and three women receiving etidronate and placebo, respectively, had a radiographic vertebral fracture. The evidence is very uncertain about the effect of etidronate on radiographic vertebral fracture (RR 0.14, 95% CI 0.01 to 2.68; POR 0.13, 95% CI 0.01 to 1.27; very low-certainty evidence; Analysis 1.5).

For secondary prevention, three trials reported data for this outcome (Lyritis 1997; Watts 1990; Wimalawansa 1998), in which 15 (6.0%) women treated with etidronate 400 mg/day and 31 (13.1%) women treated with placebo sustained at least one radiographic vertebral fracture. The pooled RR 0.46 (95% CI 0.26 to 0.82) demonstrated a decreased risk (relative risk reduction (RRR) of 54% (95% CI 18% to 74%)) and number needed to treat for an additional harmful outcome (NNTH) of 14 (95% CI 10 to 42). However, we assessed the evidence as being of very low certainty; therefore, we are uncertain whether etidronate results in a clinically important reduction in radiographic vertebral fractures.

Although the evidence was of very low certainty, it did meet our threshold for clinical importance (> 15% RRR). Therefore, we calculated the absolute measures absolute risk reduction (ARR) and NNTH of their five-year risk of vertebral fracture after treatment with etidronate 400 mg/day by applying the important RRR of 54% in radiographic vertebral fractures to the women with different levels of fracture risk estimated by the FRACTURE Index (FI). Results are provided in Table 4 as well as for increasing age in Table 5. For the illustrative case of the woman with an FI of 6 to 7, the ARR in vertebral fracture was 3.8% (that is, a reduction in risk from 7.1% to 3.3%) and the NNTH was 26 (that is, 26 women need to be treated to avoid one radiographic vertebral fracture). Across the range of increasing FI risk, the ARR for radiographic vertebral fracture ranged from 0.6% to 6.0% and the NNTH to avoid one vertebral fracture ranged from 154 to 17. For the illustrative woman in the age group 60 to 64 years, the ARR for the first radiographic vertebral fracture was 0.5% (that is, a reduction in risk from 1.0% to 0.5%) and the NNTH was 185 (that is, 185 women need to be treated to avoid the first fracture). The ARR for a subsequent fracture was 5.2% (that is, a reduction in risk from 9.7% to 4.5%) and the NNTH was 19 (that is, 19 women need to be treated to avoid one subsequent fracture). For increasing age, the five-year age-specific ARR for the first radiographic vertebral fracture increased from 0.1% for the youngest age group (50 to 54 years) to 2.5% in the highest age group (90+ years) and the NNTH decreased from 926 to 39. For subsequent fractures, ARR increased from 0.3% to 15.1% and the NNTH decreased from 370 to 7.

Gastrointestinal adverse events

Data were available in one primary study only (Herd 1997). Nine of 74 women (12.2%) receiving etidronate and 17 of 77 receiving placebo (22.4%) reported gastrointestinal incidents. Etidronate appeared to result in fewer gastrointestinal adverse events, but the CI of the effects included no effect (RR 0.54, 95% CI 0.26 to 1.14; Analysis 1.8).

Atypical femoral fracture

Two primary (Pouilles 1997; Montessori 1997) and one secondary prevention study (Lyritis 1997) provided evidence. Zero incidents were reported across the studies, so no RR was estimable. In total, 144 participants were treated with etidronate, of which 94 women received etidronate for two to three years for primary prevention and 50 women for four years for secondary prevention (Analysis 1.9).

Narrative description of other results

One two-year secondary prevention trial, Watts 1990, reported major outcomes for its two extension periods, the second of which (Miller 1997) re-randomized the participants (46%, 193/423) after their continuous exposure to etidronate in the first four-year open-label extension (Harris 1993). Although the reported data appeared eligible for quantitative analysis, including it in the analysis along with Watts 1990 would result in the double counting of participants and risk dependency between the two data sets. We therefore chose to describe the data narratively. During the two-year extension, four (5.3%) and 14 (18.4%) women receiving etidronate, and 14 (15.6%) and 13 (14.4%) women receiving placebo experienced at least one radiographic vertebral and non-vertebral fracture, respectively. Nine women in the etidronate (9.7%) and seven (7.0%) in the placebo group discontinued due to adverse events (Analysis 1.9).

Comparison 2. Etidronate 200 mg/day versus placebo

Data for lower daily etidronate (200 mg) compared to placebo was scant. None of the included studies used etidronate 200 mg/day for primary prevention. For secondary prevention, only three studies reported at least one outcome of interest (Ishida 2004; Iwamoto 2001; Shiota 2001).

Major outcomes

Three studies with a total of 111 women assigned to etidronate and 110 to the placebo group provided limited data (Ishida 2004; Iwamoto 2001; Shiota 2001). None of the included studies reported clinical vertebral fractures or non-vertebral fractures.

For hip fractures (Analysis 11.1), etidronate's effects compared with placebo varied, with a wide CI (0% versus 1.1%; RR 0.33, 95% CI 0.01 to 8.04; POR 0.14, 95% CI 0.00 to 6.82). For wrist fractures, zero incidents were reported, and the effect size was not estimable.

Each of the remaining two major outcomes, withdrawals due to adverse events and serious adverse events, was reported by one secondary prevention study. Ishida 2004 reported that one and zero women receiving etidronate 200 mg/day and placebo, respectively, discontinued the study because of adverse events. The estimate RR was 3.00 (95% CI 0.12 to 72.33; Analysis 1.6).In Shiota 2001, zero of 20 women in each of the etidronate 200 mg/day and placebo groups experienced a serious adverse event, so the RR was not estimable (Analysis 1.7).

Minor outcomes

Three minor outcomes were reported in three studies for secondary prevention (Ishida 2004; Iwamoto 2001; Shiota 2001). The results are provided in Table 3.

Radiographic vertebral fractures

Etidronate 200 mg/day was observed to result in an important risk reduction. In total, three studies reported that 11 (9.9%) and 34 (30.9%) women in the etidronate and placebo groups, respectively, sustained a fracture (Ishida 2004; Iwamoto 2001; Shiota 2001). The estimate of the RR was 0.32 (95% CI 0.17 to 0.60; Analysis 11.3).

Corresponding to the important RRR of 68% observed for etidronate 200 mg/day in radiographic vertebral fractures, the absolute measures ARR and NNTH of the five-year risk of radiographic vertebral fracture after treatment with etidronate were calculated (expected) for different levels of increasing risk as given by the FI. Results are provided in Table 4 as well as for increasing age in Table 5. For the illustrative case of the woman with an FI of 6 to 7, the ARR in radiographic vertebral fracture was 4.8% (that is, a reduction in risk from 7.1% to 2.3%) and the NNTH was 21 (that is, 21 women need to be treated to avoid one radiographic vertebral fracture). Across the range of increasing FI risk, the ARR for vertebral fracture ranged from 0.8% to 7.6% and the NNTH to avoid one radiographic vertebral fracture ranged from 123 to 13. For the illustrative woman in the age group 60 to 64 years, the ARR for the first radiographic vertebral fracture was 0.7% (that is, a reduction in risk from 1.0% to 0.3%) and the NNTH was 147 (that is, 147 women need to be treated to avoid the first fracture). The ARR for a subsequent fracture was 6.6% (that is, a reduction in risk from 9.7% to 3.1%) and the NNTH was 15 (that is, 15 women need to be 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) to 3.2% in the highest age group (90+ years) and the NNTH decreased from 735 to 31. For subsequent fractures, ARR increased from 0.3% to 19.0% and the NNTH decreased from 294 to 5.

Gastrointestinal adverse events

Data were only available in one secondary prevention study (Iwamoto 2001). Five of 25 women (20.0%) receiving etidronate and two of 24 receiving placebo (8.3%) experienced at least one gastrointestinal adverse event. The estimate RR was 2.40 (95% CI 0.51 to 11.21; Analysis 11.6).

Atypical femoral fracture

None of the primary prevention studies reported this outcome. For secondary prevention, two studies including a total of 91 women treated with etidronate and 90 with placebo reported zero incidents (Analysis 11.7).

Subgroup analyses

To explore whether etidronate's anti-fracture effects differ by treatment duration or participants' prior experiences with bisphosphonates, we conducted the following two subgroup analyses.

Etidronate 400 mg/day versus placebo

Different treatment durations

We conducted separate analyses for treatment durations lasting one (Analysis 2.1), two (Analysis 3.1 to Analysis 3.4), three (Analysis 4.1 to Analysis 4.4), and four years (Analysis 5.1 to Analysis 5.4), all of which are summarized in Table 6.

For primary prevention, no study provided one-year data. Three studies (Herd 1997; Meunier 1997; Pouilles 1997) and one study (Montessori 1997) reported outcomes for the two-year and three-year time points, respectively. In most cases, these time points corresponded to the length of the study, so that the evidence broken down by treatment duration was the same as at the end of the study in the base case analysis. Therefore, the effects of etidronate by year were not different from what had been observed in the base case: etidronate appeared to make little or no difference to clinical vertebral, non-vertebral, hip, and radiographic vertebral fractures, after two years of treatment; and to hip and radiographic vertebral fractures after three years of treatment. None of the studies provided data on wrist fractures.

Of four secondary prevention studies reporting fracture outcomes, one, one, and two provided two-year (Watts 1990), three-year (Storm 1990), and four-year treatment data (Lyritis 1997; Wimalawansa 1998), respectively. Based on the limited evidence, etidronate was only observed to make an important difference to radiographic vertebral fractures after two (RR 0.33, 95% CI 0.17 to 0.67 (Lyritis 1997; Watts 1990)) and three years of treatment (RR 0.29, 95% CI 0.10 to 0.82 (Lyritis 1997)). For four years, there was either no evidence or etidronate appeared to make little or no difference to non-vertebral, hip, and wrist fractures. None of the studies provided data for clinical vertebral fractures.

Prior bisphosphonate experience

Due to the poor reporting on participants' prior treatment in the base case scenario, only two primary (Herd 1997; Meunier 1997) and three secondary prevention studies (Storm 1990; Watts 1990; Wimalawansa 1998) reporting any fracture outcome data could be identified as recruiting bisphosphonate-naïve participants exclusively (Analysis 6.1 to Analysis 6.5; Table 6). None of the included studies focused on bisphosphonate-experienced participants alone.

For bisphosphonate-naïve women treated for primary prevention, etidronate's effects were uncertain for clinical vertebral (RR 3.00, 95% CI 0.13 to 70.53) and non-vertebral fractures (RR 0.67, 95% CI 0.12 to 3.68), not reported for hip and wrist fractures, and not estimable for radiographic vertebral fractures. For women who had never been exposed to any bisphosphonate and were treated for secondary prevention, we do not know if etidronate makes a difference to non-vertebral fractures (RR 1.14, 95% CI 0.75 to 1.73), hip (RR 2.97, 95% CI 0.12 to 72.12), and wrist fractures (inestimable RR), and we do not have any evidence for clinical vertebral fractures. However, etidronate resulted in a risk reduction in radiographic vertebral fractures for secondary prevention compared with placebo (52%; RR 0.48, 95% CI 0.24 to 0.96), which may be less important compared to that of the base case (54%; RR 0.46, 95% CI 0.26 to 0.82).

Etidronate 200 mg/day versus placebo

To investigate the anti-fracture effects of etidronate 200 mg/day for different treatment durations and for participants' prior bisphosphonate experience, the following subgroup analyses were conducted for three secondary prevention trials which reported at least one fracture outcome (Ishida 2004; Iwamoto 2001; Shiota 2001). The results are summarized in Table 7.

Different treatment durations

For the one-year time point, evidence was only available for one study reporting radiographic vertebral fractures (Ishida 2004), in which 7.6% of the women receiving etidronate 200 mg/day and 13.6% of the women receiving placebo experienced at least one incident. The estimated RR 0.56 (95% CI 0.20 to 1.57) indicated that one year of etidronate 200 mg/day may reduce radiographic vertebral fractures. However, the CI of the estimated effects includes no effect, and it is possible that etidronate might make or

little difference to this outcome (Analysis 12.1). There were no data reported for other fracture outcomes at year one.

All three secondary prevention studies had two-year treatment durations (Ishida 2004; Iwamoto 2001; Shiota 2001). Therefore, etidronate's anti-fracture effects after two years were the same as those observed in the base case analysis, which pooled the evidence at the longest time point. In summary, the effects of etidronate 200 mg/day might make little or no difference to hip fractures, are not estimable for wrist fractures, and result in an important risk reduction for radiographic vertebral fractures (RRR 68%, 95% CI 40% to 83%;Analysis 13.1 toAnalysis 13.3).

Prior bisphosphonate experience

Of the three secondary prevention trials available for the 200 mg/day base case analysis, only one had exclusively recruited bisphosphonate-naïve participants (Iwamoto 2001), while none had exclusively recruited bisphosphonate-experienced participants. For women who were at higher fracture risk and who had never been exposed to any bisphosphonate, zero hip or wrist fractures occurred in the only trial, so the effect size was not estimable. However, two of 25 women treated with etidronate 200 mg/day and six of 24 with placebo sustained a radiographic vertebral fracture. The estimated RR 0.32 (95% CI 0.07 to 1.43) indicated that etidronate 200 mg/day might make little or no difference in the prevention of radiographic vertebral fractures (Analysis 14.1 to Analysis 14.3).

Sensitivity analyses

Etidronate 400 mg/day versus placebo

To test the robustness of anti-fracture results of etidronate 400 mg/day in the base case analyses, we conducted the following sensitivity analyses, all of which are summarized in Table 8.

Follow-up versus baseline denominators

We used baseline denominators (randomised numbers) for women taking etidronate 400 mg/day and placebo for the relative risk calculation of fracture outcomes, and compared these with the results from the base case analysis using follow-up denominators. As summarized in Table 8, the use of baseline denominators either slightly increased or did not change the sample size included in the quantitative analyses, which made little or no differences to the estimates of the RRs of etidronate's anti-fractures effects in terms of direction, magnitude, and precision. The results of the base case analysis appear robust regardless of which type of denominator is used. (See Analysis 7.1 to Analysis 7.5.)

Studies with fracture as an efficacy outcome

Of the studies in the base case analyses, two of four primary (Herd 1997; Montessori 1997) and all four secondary prevention trials (Lyritis 1997; Storm 1990; Watts 1990; Wimalawansa 1998) identified fractures as efficacy outcomes. In these trials, the fracture outcomes were well-defined and confirmed by radiographic or morphometric methods, and/or the statistical strategy was pre-planned appropriately for hypothesis testing. For primary prevention, the loss of two studies resulted in no remaining evidence for clinical vertebral and non-vertebral fractures originally observed in the base case. The RRs for hip and radiographic vertebral and non-vertebral fractures, however, remained the same as those in the base case.

On the whole, the results appeared robust regardless of the fracture outcomes being investigated as efficacy outcomes. The robustness of etidronate's anti-fracture effects on clinical vertebral and non-vertebral fractures, nevertheless, could not be investigated due to the paucity of evidence. (See Analysis 8.1 to Analysis 8.4.)

Studies with high methodological quality

None of the primary and secondary prevention studies included in the base case analysis were assessed as being of high methodological quality. A sensitivity analysis was not required.

Analysis excluding primary/secondary prevention studies classified on age alone

Of the studies included in the base case analyses, only two were defined as primary prevention based entirely on age, due to lack of other information (Montessori 1997; Pouilles 1997). The evidence excluding those two studies led to different estimates for etidronate's anti-fracture effects (versus those estimated in the base case): clinical vertebral fractures, RR 3.00, 95% CI 0.13 to 70.53 (versus RR 3.03, 95% CI 0.32 to 28.44), non-vertebral fractures, RR 0.56, 95% CI 0.20 to 1.61 (versus RR 0.67, 95% CI 0.12 to 3.68), and radiographic vertebral fractures, inestimable RR (versus RR 0.14, 95% CI 0.01 to 2.68). There appeared to be no noticeable differences between the estimates of the RRs from the two scenarios. The results of the base case remained robust regardless of the lone use of the arbitrary criterion, age. (See Analysis 9.1 to Analysis 9.5).

Analysis excluding studies using an ADFR regimen

There were no ADFR regimens in primary prevention, so a sensitivity analysis was not required.

For secondary prevention, two studies incorporated intermittent/cyclic etidronate into the ADFR regimen using different approaches (Lyritis 1997; Watts 1990). In each 85-day cycle over four years, Lyritis 1997 used the activator 1,25-dihydroxyvitamin D_3 (2 µg/day) for five days, followed by etidronate 400 mg/day plus calcium 500 mg/day for 20 days and then calcium 500 mg/day for 65 days. Watts 1990, however, used phosphate 1 g twice a day for three days as the activator, followed by 14-day etidronate 400 mg/day and then calcium 500 mg/day for 74 days. The 91-day cycle was repeated for two years. Given the factorial design in this study, two of the four arms which used a placebo activator were still regarded as intermittent/cyclic etidronate, so were excluded in the sensitivity analyses.

The exclusion of the ADFR evidence resulted in estimates that were different from the base case. For non-vertebral, hip, and wrist fractures, the estimates of the RR versus those in the base case were 1.13 (95% CI 0.67 to 1.88) versus 1.07 (95% CI 0.72 to 1.58), 2.97 (95% CI 0.12 to 72.12) versus 0.93 (95% CI 0.17 to 5.19) and an inestimable RR versus 0.90 (95% CI 0.13 to 6.04), respectively. For radiographic vertebral fractures, the important risk reductions (RRR 54%, 95% CI 18% to 74%) were no longer observed. Instead, the estimated RR 0.52 (95% CI 0.23 to 1.16) indicated that etidronate might make little or no difference. Although etidronate's anti-fracture effects were inconclusive for these three outcomes in both the base case and sensitivity analyses, the effect sizes estimated in the latter indicated potentially higher risk (albeit with less precision) with etidronate treatment. The robustness of etidronate's anti-fracture effects for secondary prevention was challenged. (See Analysis 10.1toAnalysis 10.5.)

Etidronate 200 mg/day versus placebo

No trial used 200 mg/day for the primary prevention of fractures. The robustness of anti-fracture results of etidronate 200 mg/day for secondary prevention in the base case were tested in the following sensitivity analyses (Table 7).

Follow-up versus baseline denominators

All three of the secondary prevention trials included in the base case had the same follow-up and randomised denominators, so the estimates of the RRs were the same as those calculated for the base case. The effects of etidronate 200 mg/day on benefit outcomes are robust to the choice of denominator. (See Analysis 15.1 to Analysis 15.3.)

Studies with fracture as an efficacy outcome

Only two of the three trials identified fractures as efficacy outcomes (Ishida 2004; Iwamoto 2001). The removal of the Shiota 2001 study did not change the results of hip fractures but resulted in an estimated RR 0.43 (95% CI 0.22 to 0.85) for radiographic vertebral fractures. Compared to the estimated RR (0.32, 95% CI 0.17 to 0.60) in the base case, both estimates indicate an important risk reduction (RRR 57% (95% CI 15% to 78%) versus 68% (95% CI 40% to 83%)). The base case results appear robust regardless of whether the included studies identified fracture outcomes as efficacy outcomes. (See Analysis 16.1 to Analysis 16.3.)

Remaining sensitivity analyses

The remaining prespecified sensitivity analyses (for methodological quality; study classification based on age alone; use of an ADFR regimen) were not required, as none of the three secondary prevention studies included in the base case analysis had these characteristics.

Comparison 3. Etidronate versus other anti-osteoporotic agents

Etidronate (400 mg or 200 mg) alone was most frequently compared to alendronate (Iwamoto 2005; Köşüş 2005; Russo 1996; Sahota 2000) and hormone replacement therapy (HRT) (Ishida 2004; Wimalawansa 1995; Wimalawansa 1998). As one of the early anti-osteoporotic drugs, the benefits and harms of etidronate combined with other anti-osteoporotic agents, including HRT (Wimalawansa 1995; Wimalawansa 1998), calcitriol (Gürlek 1997), and alfacalcidol (Iwamoto 2003b), were also investigated. In total, one primary (Wimalawansa 1995) and 13 secondary prevention studies (Fukunaga 2002; Guañabens 2000; Gürlek 1997; Ishida 2004; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Masud 1998; Russo 1996; Sahota 2000; Watts 1990; Wimalawansa 1998) providing active comparisons to etidronate (alone or in combination) reported at least one outcome of interest. Except for withdrawals due to adverse events, which was reported by the only primary prevention study, the evidence for major outcomes is from secondary prevention.

Major outcomes

Clinical vertebral fractures

None of the included studies reported this outcome except for one three-arm study (Russo 1996), which provided two pair-wise comparisons of etidronate 400 mg/day versus alendronate 5 mg/day and intermittent/cyclic clodronate. However, zero fractures were reported, so the effect size was inestimable. (See Analysis 17.1; Appendix 5.)

Non-vertebral fractures

Six secondary prevention studies provided 13 pair-wise comparisons of etidronate in different dose regimens, three of which reported zero incidents, including the comparisons of etidronate 400 mg/day versus alendronate 5 mg/day or intermittent/cyclic clodronate (Russo 1996), and etidronate 200 mg/day versus alendronate 5 mg/day (Iwamoto 2005).

The ten remaining comparisons with estimable RRs were based on single study data. Little or no difference was observed for the following:

- etidronate 400 mg/day compared with fluoride 50 mg/day (RR 0.66, 95% CI 0.23 to 1.86 (Guañabens 2000)), HRT (RR 1.06, 95% CI 0.07 to 15.62 (Ishida 2004)), and etidronate 400 mg/day plus HRT (RR 1.12, 95% CI 0.08 to 16.52 (Wimalawansa 1998));
- etidronate 200 mg/day compared with risedronate 2.5 mg/day (RR 0.58, 95% CI 0.17 to 1.92 (Fukunaga 2002)), alfacalcidol 1 µg/day (RR 1.00, 95% CI 0.06 to 15.65 (Ishida 2004)), weekly intravenous calcitonin 20 IU (RR 3.00, 95% CI 0.12 to 72.33 (Ishida 2004)), HRT (RR 3.00, 95% CI 0.12 to 72.33 (Ishida 2004)), and menatetrenone 45 mg/day (RR 3.00, 95% CI 0.12 to 72.33 (Ishida 2004));
- etidronate 400 mg/day plus HRT compared with placebo (RR 0.95, 95% CI 0.06 to 14.04 (Wimalawansa 1998)) and HRT (RR 0.95, 95% CI 0.06 to 14.04 (Wimalawansa 1998)).

(See Analysis 18.1; Appendix 5.)

Hip fractures and wrist fractures

One Italian and four Japanese studies providing active treatment comparisons to etidronate reported zero hip and wrist fractures. The effect sizes for the eight pair-wise comparisons were not estimable, including etidronate 400 mg/day versus alendronate 5 mg/day (Russo 1996) and intermittent/cyclic clodronate (Russo 1996); and etidronate 200 mg/day versus alendronate 5 mg/day (Iwamoto 2005), alfacalcidol 1 µg/day (Ishida 2004), weekly intravenous calcitonin 20 IU (Ishida 2004), HRT (Ishida 2004), menatetrenone 45 mg/day (Ishida 2004; Iwamoto 2001), and etidronate 200 mg/day plus alfacalcidol 1 µg/day (Iwamoto 2003b). (For hip fracture, see Analysis 19.1; for wrist fracture, see Analysis 20.1; Appendix 5.)

Withdrawals due to adverse events

For primary prevention, only one four-arm study reported this outcome (Wimalawansa 1995). Little or no risk difference was observed for all four pair-wise comparisons of interest, including etidronate 400 mg/day versus HRT (RR 1.07, 95% CI 0.17 to 6.61); etidronate 400 mg/day plus HRT (RR 1.07, 95% CI 0.17 to 6.61); as well as etidronate 400 mg/day plus HRT versus placebo (RR 0.62, 95% CI 0.12 to 3.19); and HRT (RR 1.00, 95% CI 0.16 to 6.20). (See Analysis 22.1.)

For secondary prevention, we extracted 20 pair-wise comparisons related to etidronate from 10 studies. Most of the results were estimated from single study data. Etidronate 400/day appeared to decrease the risk of withdrawals due to adverse events compared to daily alendronate 10 mg (0% versus 14.8%; RR 0.11, 95% CI 0.01 to 0.79) (Köşüş 2005; Sahota 2000), and fluoride 50 mg (4.8% versus 23.6%; RR 0.20, 95% CI 0.06 to 0.67) (Guañabens 2000),

although all the confidence intervals appeared wide. (See Analysis 22.2;Appendix 6.)

None of the remaining comparisons, including six reporting zero incidents for all participants, demonstrated a risk difference between etidronate-related interventions and comparators. The details are summarized in Appendix 6.

Serious adverse events

Three secondary prevention studies provided four comparisons: etidronate 400 mg/day compared with an ADFR regimen (Steiniche 1991), alendronate 5 mg/day (Russo 1996), and intermittent/cyclic clodronate (Russo 1996); and etidronate 200 mg/day compared with alendronate 5 mg/day (Iwamoto 2005). However, zero incidents were reported across studies and no RR was estimable. (See Analysis 23.1; Appendix 6).

Minor outcomes

Radiographic vertebral fractures

Eight secondary prevention studies providing 14 pair-wise active treatment comparisons reported this outcome. All but one were based on single study data. When pooled, little or no difference was observed between etidronate 200 mg/day and menatetrenone 45 mg/day (11.0% versus 12.4%; RR 0.89, 95% CI 0.40 to 2.00) (Ishida 2004; Iwamoto 2001). The effect sizes of three comparisons including etidronate 400 mg/day versus alendronate 5 mg/day (Russo 1996) and intermittent/cyclic clodronate (Russo 1996), as well as etidronate 200 mg/day versus alendronate 5 mg/day (Iwamoto 2005), were not estimable as there were zero incidents. None of the remaining ten comparisons indicated risk differences between the interventions and comparators. (See Analysis 21.1; Appendix 7.)

Gastrointestinal adverse events

For secondary prevention, six trials provided six pair-wise comparisons of etidronate versus other anti-osteoporotic agents. All the risks were estimated by a single study, none of which indicated a risk difference between the treatment and comparator, including etidronate 400 mg/day versus ADFR (RR 4.75, 95% CI 0.24 to 92.65 (Steiniche 1991)) and fluoride 50 mg/day (RR 0.55, 95% CI 0.27 to 1.11 (Guañabens 2000)), as well as etidronate 200 mg/day versus alendronate 5 mg/day (RR 2.00, 95% CI 0.19 to 20.67 (Iwamoto 2005)), risedronate 2.5 mg/day (RR 0.86, 95% CI 0.52 to 1.41 (Fukunaga 2002)), menatetrenone 45 mg/day (RR 10.15, 95% CI 0.59 to 174.03 (Iwamoto 2001)), and etidronate 200 mg/day plus alfacalcidol 1 µg/day (RR not estimable for zero incidents (Iwamoto 2003b)). (See Analysis 24.1; Appendix 7.)

Atypical femoral fracture

For this rare outcome, three secondary prevention studies provided six pair-wise comparisons, all of which reported zero incidents, so none of the effect sizes were estimable. In total, 31 and 91 women who had ever been exposed to etidronate 400 mg/day for two years and etidronate 200 mg/day for one year, respectively, did not experience this outcome. (See Analysis 25.1;Appendix 7).

DISCUSSION

Summary of main results

We included 30 studies in this update review, 26 of which provided data suitable for quantitative analysis. The studies compared cyclic etidronate (400 or 200 mg/day) to placebo/no intervention or to other anti-osteoporotic drugs. We used hierarchical classification criteria based on participants' risk of fractures to distinguish between nine primary prevention studies (involving 740 women) and 17 secondary prevention studies (involving 2030 women).

The base case results for the main review comparison consisted of nine primary (740 participants) and four secondary prevention studies (667 participants) comparing etidronate 400 mg/day to placebo/no intervention across six major outcomes. Employing the GRADE approach (Summary of findings and assessment of the certainty of the evidence), we assessed the evidence as ranging from moderate to very low certainty. For primary prevention, we collected evidence from nine studies ranging from one to four years in duration. Etidronate may make little to no difference to four major outcomes, including non-vertebral fractures and serious adverse events (moderate certainty), and clinical vertebral fractures and withdrawals due to adverse events (low certainty). Its effects on hip fractures were not estimable (very low-certainty evidence) and not measured/reported for wrist fractures. For secondary prevention, four studies comparing etidronate with placebo/no intervention and ranging from two to four years in duration contributed to the outcome data. The evidence indicated that etidronate may result in little to no difference in non-vertebral fractures (low-certainty evidence). We do not know the effects of etidronate on hip and wrist fractures, withdrawals due to adverse events, and serious adverse events, all of which were estimated by very-low certainty evidence. None of the secondary prevention studies reported clinical vertebral fractures.

Regarding the three minor outcomes with evidence, etidronate was only observed to result in a clinically important risk reduction (RRR 54%, 95% CI 18% to 74%) for radiographic vertebral fractures; however, this result is uncertain due to the very low-certainty evidence. For gastrointestinal adverse events, etidronate appears to make little or no difference for primary prevention, and there was no evidence available for secondary prevention. For atypical femoral fractures, zero incidents were reported, and the effects were not estimable for both primary and secondary prevention.

The lower daily dose of etidronate (200 mg/day) was less frequently investigated for secondary prevention and not at all for primary prevention. The limited data only demonstrated that etidronate is better than placebo in preventing radiographic vertebral fractures, with a risk reduction of 68% (RR 0.32, 95% CI 0.17 to 0.60). It appears to make little or no difference to hip fractures and gastrointestinal adverse events. Zero wrist and atypical femoral fractures were reported, and the effects were not estimable. Etidronate's effects on the remaining major and minor outcomes of interest were not reported.

No direct comparison of etidronate at different daily doses was observed. When compared with other anti-osteoporotic drugs, alendronate was the most frequently investigated, followed by HRT alone and etidronate with an add-on of HRT or menatetrenone. There appeared to be no difference in benefits or harms observed between etidronate and other anti-osteoporotic drugs.

Overall completeness and applicability of evidence

This review summarizes findings from 26 studies conducted between 1990 and 2005. Of the 16 studies which reported participants' ethnicity/race, white and Asian women accounted for most of the participants. Twenty-five studies (96%) were conducted within a single country, comprising 20 single-centre studies and five studies employing a multicenter design. We included both naturally and surgically menopausal women. The ranges of the participants' baseline age (49 to 72 years old) and BMD T-scores were broad (femoral neck: -0.95 to -2.80; lumbar spine: -1.04 to -3.30). To ensure that participants in the primary and secondary prevention studies were representative of women at lower (normal BMD and osteopenia) and higher risk (osteoporosis) of fractures, respectively, we applied a hierarchical classification algorithm. We developed the algorithm through a peer-reviewed consensus process based on WHO diagnostic criteria for osteoporosis, lending it both content and face validity. Its criterion validity was partly supported by the fact that the risk of radiographic vertebral fractures for women receiving placebo in the secondary prevention studies was indeed higher than that of the placebo groups in primary prevention studies (primary 2.6% versus secondary 13.1%; P value (two-tailed probability) = 0.0018). The risk comparisons of other fracture outcomes were, however, modest due to the lack of evidence, including clinical vertebral fractures (primary 0% versus secondary not reported; not testable); non-vertebral fractures (primary 11.0% versus secondary 12.8%; P value = 0.6604), hip fractures (primary 0% versus secondary 1.3%; P value = 0.1667), and wrist fractures (primary not reported versus secondary 2.4%; not testable). The categorization of primary and secondary studies was performed in duplicate (CZ and SH), and conflicts were resolved by a third review author when needed (GW or JP). The separate presentation of evidence for primary and secondary prevention can help stakeholders in making decisions tailored to the fracture risk of the targeted population across a range of pertinent outcomes, including six major and three minor outcomes available in this review.

We applied a clinically important reduction of greater than 15% in presenting the evidence for benefit outcomes. This approach not only avoids the P value fallacy(Dixon 2003a), but is in agreement with the reporting practice recommended by Cochrane (Schünemann 2022b). We assessed the importance of fracture risk reduction and the precision of the estimates based on the likelihood that clinicians would make a different decision if the true effect was near one end of the 95% confidence interval or the other (Schünemann 2022a).

In addition, we did not limit our literature search by language, date, form of publication, or inclusion of outcomes of interest. The external generalizability of the findings appears to support the applicability of the evidence.

Certainty of the evidence

Following the GRADE approach (GRADEpro GDT; Schünemann 2022b), we constructed two summary of findings tables for intermittent/cyclic etidronate 400 mg/day used for primary and secondary prevention, respectively. Each table included four benefit outcomes (fractures) and two harm outcomes (withdrawals due to adverse events and serious adverse events). In this review, we only included randomized controlled trials.

For all outcomes with available evidence, we did not detect any publication bias in our analyses, which was mainly based on the symmetrical distributions of the effect estimates. In general, imprecision emerged as a primary limiting factor across all assessed outcomes for not meeting the optimal information size (OIS) criteria. Specifically, for fracture outcomes, the 95% CI of the estimated effect sizes encompassed both "no effect" (RR = 1) and our predefined "clinically important effect threshold" (a 15% relative change; RR = 0.85). Additionally, certain evidence was downgraded for indirectness due to the inclusion of studies employing an ADFR regimen with etidronate administered following an activator. Where applicable, we acknowledge the potential bias of the prior addition of an "activator" in each cycle on the benefit and harm effects of etidronate. Both limiting factors led to a one- or two-level downgrade in the evidence.

In summary, the evidence for etidronate 400 mg/day in primary prevention exhibits slightly higher certainty compared to that in secondary prevention. Indirectness served as the primary reason for further downgrading in the secondary prevention studies. None of the primary and secondary prevention studies, respectively, reported wrist fractures and clinical vertebral fractures.

Potential biases in the review process

To minimize the possibility of introducing bias, we followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* and referred to the *Methodological Expectations of Cochrane Intervention Reviews* (MECIR) standards and relevant materials to avoid common errors (Higgins 2022; Higgins 2023). We employed several approaches to address the potential limitations of the review process. To capture the eligible studies, a second information specialist conducted an independent review of the search strategy, following the Peer Review of Electronic Search Strategies (PRESS) guidelines (McGowan 2016). We did not exclude studies on the basis of language, date, or form of publication, or the lack of a usable outcome of interest. Along with duplicate study screening and selection, data extraction, and risk of bias assessment, we used DistillerSR software (DistillerSR) to ensure the independence, impartiality, and inter-reliability of review authors, while securely storing materials for future research.

However, we acknowledge the following potential sources of biases. First, we only included RCTs lasting longer than one year; therefore, we might have overlooked short-term safety issues for etidronate. Nevertheless, we measured the harms frequently related to bisphosphonate use, including gastrointestinal adverse events, atypical femoral fractures, and osteonecrosis of the jaw. The review's outcomes of withdrawals due to adverse events and serious adverse events were used indirectly to observe some of the intolerable events that may occur within the first year of treatment. Given the results that etidronate-treated participants did not have a risk increase in the occurrence of withdrawals due to adverse events and serious adverse events, the short-term safety events of etidronate that might have been missed were probably tolerable and transient. Second, the cyclical use of etidronate differed from study to study. Due to the limited evidence, we were unable to investigate whether the lengths of the off-treatment periods, which ranged from 60 to 91 days, might affect the estimates of etidronate's benefits and harms. In addition, two secondary prevention studies adopted an ADFR approach, in which an activator was used (Lyritis 1997; Watts 1990). The sensitivity analyses excluding these studies failed to

confirm the robustness of the base case results for radiographic vertebral, hip, and wrist fractures, given the insufficient evidence that remained. Third, we aimed to collect high-quality evidence from RCTs, so we only extracted data from the periods in which the randomly assigned treatments were maintained. For example, we did not extract data from the open-label extension (year 4-5) of the Watts 1990 study because the original randomization was broken, and all participants received etidronate throughout the extension period. Fourth, although regarded as background medications whose effectiveness is unclear, the use of calcium or vitamin supplementation, or both, varied notably by study (including no supplementation at all, use of vitamin D derivatives, or dietary intake) and in duration (continuously or intermittently for off-treatment periods). Fifth, the unit of measurement for dichotomous outcomes was the number of participants with the event (incident) instead of the number of events. Although the incidence better conveys the risk of the occurrence of outcome and was more frequently reported, we did lose some data as a result of this approach. For example, we did not include Pacifici 1988 in the quantitative synthesis because it only reported the total fractures instead of the number of women sustaining the fractures. Another study reported the numbers of individual gastrointestinal symptoms which could not be added up to form a composite outcome of 'number of participants experiencing at least one gastrointestinal adverse event', since any of the participants could have complained of more than one symptom (Pouilles 1997). However, data that were not extractable or inferable were relatively rare and were recorded in our database. Finally, there are underlying limitations in evaluating safety outcomes based on summary meta-analyses of RCTs, which may include healthier participants with fewer comorbid diseases and having shorter follow-ups. The RCT safety evidence for etidronate, especially regarding the rare and more recently observed adverse events (relevant to bisphosphonates), was unavailable after the early 2000s.

Agreements and disagreements with other studies or reviews

This update supports the key findings of the first version of this review, which included and analysed only placebo-controlled trials of etidronate (Wells 2008a). Given that the latest placebo-controlled trial of etidronate was published in 2001 (Shiota 2001), we did not add much new evidence, and most of it concerned adverse events extracted from trials which did not report or measure fracture outcomes (Adami 2000; Chilibeck 2002; Heath 2000; Tobias 1997). In this update, we applied an adjusted hierarchical classification to distinguish primary and secondary prevention studies, which meant that the women in the secondary prevention studies in this review update were at a higher fracture risk than in the previous review: specifically, in this update, women in secondary prevention studies would have had a baseline BMD T-score at any measured site of -2.5 or lower (versus -2.0 or lower) and were 75 years or older (versus older than 62 years). This adjustment resulted in Montessori 1997, classified as a secondary prevention study in the previous review, being re-classified as a primary prevention study in this update, although the shift did not make a notable change in the results. Regarding the comparison of etidronate to other active agents, the evidence was limited and the most recent study we found was published in 2005.

With respect to other bisphosphonate reviews, some network meta-analyses combining direct and indirect evidence for bisphosphonates and anti-reabsorptive agents have not included etidronate (Barrionuevo 2019; Chandran 2019; Ellis 2014; Liu 2018; Migliore 2013). For those that did include etidronate (Hopkins 2011; Jansen 2011; Yang 2016a; Zhou 2016), a comparison of our results with theirs was hindered by different study scopes and analytic strategies. The most notable difference is that these reviews targeted postmenopausal women who had a diagnosis of osteoporosis, whereas our population included postmenopausal women at different risks of fracture. This might result in their omission of trials recruiting postmenopausal women who were at lower risk of fractures (i.e. some of the nine primary prevention trials included in our review) and who were at higher risk of fracture but had not received a formal diagnosis (e.g. one out of 17 included secondary prevention trials defined by the criteria other than diagnosis in our review). In addition, some of the reviews including etidronate also restricted trial inclusion on criteria such as reported outcomes (Hopkins 2011; Yang 2016a; Zhou 2016), published form or language (i.e. full-text publications, in English) (Jansen 2011; Zhou 2016), or sample size (Yang 2016a). Our review included the largest number of RCTs, given that our only study restriction was that they had a follow-up of greater than one year.

Hopkins 2011 was the only review which targeted all postmenopausal women, as we did, but it limited inclusion based on reported outcomes (fractures as a primary or secondary outcome). From a search up to 2009, it included eight of the 30 studies included in our review. Specifically, it included three of nine primary prevention studies (Meunier 1997; Montessori 1997; Pouilles 1997), and four of 17 secondary prevention studies in its quantitative synthesis (Lyritis 1997; Storm 1990; Watts 1990; Wimalawansa 1998), as well as one secondary prevention study not included in our analysis since the data were reported as number of fractures (Pacifici 1988). Hopkins and colleagues' estimated benefits for etidronate versus placebo using a classical meta-analysis approach were different from ours when we combined the evidence for primary and secondary prevention studies. For example, the estimated odds ratios (ORs) for non-vertebral, hip, and wrist fractures were 0.64 (95% credible interval (CrI) 0.31 to 1.32) (versus our RR 0.98, 95% CI 0.68 to 1.42), 0.60 (95% CrI 0.14 to 2.66) (versus our RR 1.00, 95% CI 0.18 to 5.66), and 1.19 (95% CrI 0.37 to 3.80) (versus our RR 1.00, 95% CI 0.15 to 6.82), respectively. For radiographic vertebral fractures, we observed that etidronate resulted in a risk reduction (RR 0.43, 95% CI 0.24 to 0.75), whereas this was not indicated by Hopkins and colleagues' estimate for vertebral fractures (OR 0.59, 95% CrI 0.32 to 1.10). Although both reviews observed that etidronate makes little or no difference to these three outcomes, the two sets of estimates appear slightly different in the magnitude of the effect sizes. For comparisons of etidronate with other anti-osteoporotic drugs, only bisphosphonates (alendronate and risedronate) appeared in both reviews as a comparator. Little or no difference was found for all fracture outcomes in a meta-analysis or network meta-analysis approach. Regarding the active drugs which could only be indirectly compared to etidronate via a common comparator (placebo), including zoledronic acid, ibandronate, or non-bisphosphonates (e.g. teriparatide, raloxifene, denosumab, strontium), Hopkins 2011 did not observe different risks for vertebral fractures, non-vertebral, hip, and wrist fractures.

Both Yang 2016a and Zhou 2016, which targeted osteoporotic women within a narrower scope, also observed that, compared with placebo, etidronate made little or no difference to all fracture outcomes (non-vertebral and wrist fractures in the former, and vertebral, non-vertebral, and hip fractures in the latter), taking into consideration both direct and indirect evidence. Zhou 2016 further found that etidronate was inferior to zoledronic acid in preventing vertebral (OR 2.22, 95% CrI 1.35 to 3.70) and non-vertebral fractures (OR 1.75, 95% CrI 1.08 to 2.86), and to clodronate for non-vertebral fractures (OR 1.79, 95% CrI 1.05 to 3.03). These differences, however, were not observable in the direct comparisons in our review.

In general, etidronate did not exhibit discernible advantages across various comparator agents in our review. The lack of robust and up-to-date evidence resulted in either inestimable results or effect sizes with wide confidence intervals for both benefit and harm outcomes. From a safety perspective, etidronate, as an oral bisphosphonate, has been investigated for its link to gastrointestinal adverse events. Tadrous 2014, for example, conducted a systematic review and network meta-analysis of blinded RCTs that assessed placebo and bisphosphonates (including alendronate, etidronate, risedronate, and zoledronic acid) for osteoporosis through to 2012. Although etidronate was concluded to have the highest probability (56%) of having the greatest number of upper gastrointestinal symptoms and the highest chance (70%) of discontinuation due to an adverse event, it made little to no difference for these two outcomes when compared with placebo and other bisphosphonates. The only exception was that etidronate appeared to have higher odds of discontinuation when compared to risedronate (OR 1.61, 95% CrI 1.02 to 2.63). This difference, however, was not observed in our review. Fukunaga 2002 was the only study comparing these two bisphosphonates (but at lower daily doses), in which fewer women treated with etidronate 200 mg/day (19.7%) than those treated with risedronate 2.5 mg/day (22.9%) experienced gastrointestinal adverse events. The estimate of the RR (0.86, 95% CI 0.52 to 1.41) suggested a lower risk for etidronate, although the 95% confidence interval also indicated little or no difference between the two drugs. Our review of atypical femoral fracture revealed that no incidents were reported amongst women treated with etidronate alone or in combination with other drugs, and the effect size was not estimable. The same finding was also reported in a case-control study (Meier 2012a). Our remaining minor outcomes of interest, including health-related quality of life, acute phase reaction, osteonecrosis of the jaw, and atrial fibrillation, were not reported in any of the included studies.

AUTHORS' CONCLUSIONS

Implications for practice

Etidronate 400 mg/day does not appear to make a difference to the benefit and harm outcomes for both primary and secondary prevention of osteoporotic fractures in postmenopausal women. Although 15 years have elapsed since the first version of this review was published (Wells 2008a), there is little new evidence to shed light on the efficacy of etidronate. Etidronate appears safe for postmenopausal women; however, the evidence for starting etidronate may not be convincing. The advantages of etidronate's use – namely, its low cost and safety profile – still do not make it an optimal alternative for anti-osteoporotic care. The optimal strategy for preventing osteoporotic fractures should be in accord with a postmenopausal woman's risk of fractures and based on evidence collected for such purposes; namely, primary prevention for women with a lower risk of fractures and secondary prevention for women with a higher risk.

Implications for research

Although etidronate 400 mg/day has been recommended as an option for menopausal women who are intolerant of first-line therapies (oral bisphosphonates) for prevention of vertebral fractures (Papaioannou 2010), most of the evidence in our review came from small trials (only nine of 30 included studies included more than 100 women) which were not necessarily designed to measure fractures. Given the limited evidence of short-term harms investigated in this review, etidronate's long-term safety profile is also not clear. The insufficiency of the evidence is further limited by the lack of recent research, as there have been no trials investigating etidronate for primary or secondary prevention since 2001 and 2006, respectively. Some of the relevant systematic reviews in osteoporosis, especially the most recent ones, did not include etidronate in their scope. Our review confirms that etidronate may not be an optimal choice for anti-osteoporotic care, or an intervention of interest for further research.

However, for other bisphosphonates that are recommended as first-line or initial therapies for fracture prevention, the evolving Cochrane research methodologies used in this review could be applied to the generation of high-quality and (fracture) risk-specific evidence. As for the concern raised in observational studies regarding causal relationships between bisphosphonates and some rare but serious adverse events (including osteonecrosis of the jaw and atypical femoral fractures), direct comparison evidence is also urgently needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adami 2000

Study characteristics	
Methods	Randomized, placebo-controlled trial Primary prevention Duration: two years Blinding: double-blind Trial completion: 77/107 (72%) • Etidronate: 36/53 (68%) • Placebo: 41/54 (76%)
Participants	Inclusion criteria: postmenopausal, white, ambulatory women who had spontaneously ceased menstruation between 6 and 36 months prior to enrolment. Menopausal status was confirmed by a serum FSH level > 20 IU/L and spinal bone mineral density (L2-L4) was within 2 SD of the age-matched mean reference value. Exclusion criteria: history of alcoholism; significant psychiatric, endocrine, gastrointestinal, cardiac, renal or hepatic disease; malignancy; metabolic bone disease including a history of fragility fracture; severe degenerative disease or scoliosis of the lumbar spine or previous treatment with bone active drugs; the administration of HRT for menopausal symptoms for more than 1 year or within the previous 6 months. Age: 51.9 (3.3) years Years since menopause: 1.9 (2.5) years BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: -1.14 (1.04) Femoral neck T-score: 0.78 (0.10) Prevalent vertebral fractures: 0% Previous bisphosphonate experience: 0% Source: 6 menopausal treatment centres in Italy Race/ethnicity: Caucasian (100%)
Interventions	Two-arm comparison: • Etidronate 400 mg/day for 14 days followed by 76 days of 500 mg calcium supplements • Placebo etidronate daily for 14 days followed by 76 days of 500 mg calcium supplements
Outcomes	None of the fracture outcomes of interest were reported. Two safety outcomes were reported, including serious adverse events and withdrawals due to adverse events. Adverse events were assessed at each clinic visit after the start of treatment. A serious adverse event was defined as death, overdose, a diagnosis of cancer, any life-threatening or disabling event, or any event requiring hospitalization.
Notes	Funding information: NR
Risk of bias	

Adami 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Women were randomly allocated to receive... on a randomization code which was balanced in blocks of 4." The method for randomization code generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"a placebo-controlled, double-blind trial..." Blinding approach was not provided. It was not clear if the blinding was effective to prevent the participants and personnel from knowing the allocated interventions after assignment.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	As above: blinding approach was not provided. It was not clear if the blinding was effective to prevent the participants and outcome assessors from knowing the allocated interventions after assignment. The assessment of subjective outcomes was subject to unclear risk of bias.
Incomplete outcome data (attrition bias) Safety outcomes	High risk	"One hundred and seven women were recruited into the study, of whom 77 completed the two years of treatment (36 in the etidronate group and 41 in placebo)". The 2-year completion rates were 76% (41/54) and 68% (36/53) in the placebo and etidronate groups, respectively. We judged the study to be at high risk of attrition bias: completion rates were lower than 80% and there was insufficient information about how missing data were handled.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes appeared to be reported as described in the methods section.
Other bias	Low risk	Study appeared to be free of other risks of bias.

Chilibeck 2002

Study characteristics	
Methods	Randomized, placebo-controlled trial Primary prevention Duration: one year Blinding: double-blind Trial completion: 48/57 (84%) • Etidronate: 14/14 (100%) • Placebo: 12/14 (71%) • Etidronate plus exercise: 12/15 (80%) - not included in review • Placebo plus exercise: 10/14 (71%) - not included in review
Participants	Inclusion criteria: postmenopausal women with a cessation of menstrual bleeding for at least one year who were without factors that could affect bone mineral density. Exclusion criteria: skeletal disorders, kidney disease, or other bone-related disorders that may have an impact on normal bone metabolism. Participants with a history of chronic disease or chronic med-

Chilibeck 2002 *(Continued)*

	ication use that might influence bone metabolism or calcium balance were excluded (1 participant with Crohn's Disease was excluded), bone mineral density outside the normal reference range for age-matched controls (Z-score < -2.0); hormone replacement or bisphosphonate therapy within the past year; recent participation in a vigorous exercise program (1 participant), history of cardiovascular disease, a history of high blood pressure (above 140/90; readings in mmHg (1 mmHg = 133.322 Pa)), or any physical or orthopaedic disability (1 participant) that would place women at risk when performing exercise. Age: 57.5 (1.0) years Time since menopause: 8.2 (1.1) years BMI: 27.0 (0.7) kg/m^2 Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: -1.04 (0.19) Femoral T-score: -0.94 (0.14) Prevalent vertebral fractures: NR Previous bisphosphonate experience: NR Source: Canada Race/ethnicity: Caucasian (98%), Asian (2%)
Interventions	Two-arm comparison • Etidronate 400 mg/day for 14 days followed by 76 days of calcium carbonate 500 mg/day in a cycle that was repeated four times over 12 months • Placebo, daily calcium 500 mg All participants received daily vitamin D, 10 g (400 IU).
Outcomes	None of the fracture outcomes of interest were reported. Investigators assessed one safety outcome, withdrawals due to adverse events, but did not provide sufficient information about assessment methods.
Notes	Funded by the Health Services Utilization and Research Commission of Saskatchewan. We did not include two study arms in the quantitative analysis: etidronate plus exercise; and placebo plus exercise.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomly assigned in a double-blind fashion to four groups." A randomized trial but the method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	As above: the method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	It was a double-blind study, but the blinding approach was not provided. It is not clear if the blinding was effective to prevent the participants and personnel from knowing the allocated interventions after assignment.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	As above: the blinding approach was not provided. It is not clear if the blinding was effective to prevent the participants and outcome assessors from know-

Chilibeck 2002 *(Continued)*

		ing the allocated interventions after assignment. The assessment of subjective outcomes was subject to an unclear risk of bias.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	We extracted only one safety outcome of interest, withdrawals due to adverse events, from two of the original four arms. Twenty-six of the 28 randomized participants (93%) took the medication and were included in the analysis. We judged the study to be at low risk of bias, given the overall completion rate was better than 80%, thus the portion of missing data would less likely bias the estimate of effect size.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available, but the outcomes of interest were reported as described in the methods section. However, there seemed to be no monitoring or reporting of safety outcomes, except for withdrawals due to adverse events, which does not meet the typical reporting practice of clinical trials.
Other bias	Unclear risk	Given our research objectives, which did not include consideration of non-pharmaceutical interventions, data from two of the original four groups – placebo plus exercise; etidronate plus exercise – were not extracted. It was not clear whether the deletion of the two groups would have led to other risks of bias.

Evans 1993

Study characteristics	
Methods	Randomized, active-controlled trial Primary prevention Duration: two years Blinding: NR Trial completion: 36/46 (78%) • Etidronate: 15/NR • Etidronate + phosphate: 10/NR • Control: 11/NR
Participants	Inclusion criteria: healthy women whose menopause (defined as the cessation of menstruation for 6 months) had occurred within the previous 7 years. Exclusion criteria: systemic illness, glucocorticoid administration, ethanol > 250 g/week or cigarettes > 140/week. Age: 53.9 (3.8) years Time since menopause: 3.4 (2.3) years BMI: 24.9 (4.4) kg/m^2 Lumbar spine BMD: NR Femoral neck BMD: 0.11 (0.03) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: NR Previous bisphosphonate experience: NR

Evans 1993 *(Continued)*

	Source: Australia Race/ethnicity: NR
Interventions	Three-arm comparison: • Etidronate: 400 mg/day for 14 days every 3 months • Etidronate + phosphate: phosphate 1 g twice daily for 3 days before commencing etidronate as in group 1 • Control All participants received daily calcium 600 mg.
Outcomes	None of the efficacy outcomes of interest were reported. Two safety outcomes of interest were reported but not extractable. Gastrointestinal adverse events were reported by events number, whilst withdrawals due to adverse events were not reported by groups.
Notes	Funded by Norwich Eaton Pharmaceuticals, Clayton 3168, Australia. We did not extract any outcome data of interest. We did not include this study in the quantitative synthesis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"allocated to one of three treatment groups according to computer-generated random numbers. " The method was judged appropriate.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Incomplete outcome data (attrition bias) Safety outcomes	Unclear risk	"Thirty-six healthy women completed the 2-year study, out of an initial 46... calcium supplement thought to cause bone pain (2)... " Statistical methods for safety analysis and the numbers of the randomized participants in each group were not provided. Two safety outcomes of interest were reported but not extractable: gastrointestinal adverse events were reported by event number, and withdrawals due to adverse events were not reported by groups.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes reported in the results section were the same as described in the methods section.
Other bias	Low risk	Study appeared to be free of other risks of bias.

Fukunaga 2002

Study characteristics

Methods	Randomized, active-controlled trial Secondary prevention Duration: 48 weeks

Fukunaga 2002 *(Continued)*

	Blinding: double-masked, double-dummy Trial completion: 200/235 (85%) • Etidronate: 102/117 (87%) • Risedronate: 98/118 (83%)
Participants	Inclusion criteria: ambulatory patients of either sex, aged 40 to 75 years, with involutional osteoporosis as defined by the Committee of the Japanese Society for Bone and Mineral Research (JSBMR). JSBMR criteria were almost the same as those of the World Health Organization. Exclusion criteria: any secondary osteoporosis or other diseases with reduced bone mass, recent use of drugs known to affect bone metabolism, serious renal, hepatic or cardiac diseases, drug hypersensitivity, oesophagitis, peptic ulcer, history of radiotherapy to the lumbar spine or pelvis, and malignant tumour under treatment with antitumour agent, morphologic problems that grossly interfere with accurate L2-L4 BMD determination (e.g. severe spinal scoliosis, fracture, deformity or osteosclerotic change in L2-L4) Age: 62.6 (6.2) years Time since menopause: 13.3 (7.2) years BMI: 21.4 (2.8) kg/m^2 Lumbar spine BMD: 0.66 (0.08) g/cm^2 Femoral neck BMD: NR Lumbar spine T-score: -2.97 (0.44) Femoral neck T-score: NR Prevalent vertebral fractures: 34 (15%) Previous bisphosphonate experience: NR Source: France, the UK, the Netherlands, Belgium, and Germany Race/ethnicity: Asian (100%)
Interventions	Two-arm comparison: • Etidronate: four cycles of 2 weeks of treatment with etidronate 200 mg/day followed by 10-week medication-free periods • Risedronate 2.5 mg/day All participants received daily calcium 200 mg.
Outcomes	Radiographic vertebral fractures: assessed as an efficacy endpoint. Lateral and anteroposterior thoracic and lumbar spine radiographs were obtained at baseline and after treatment. A vertebra was considered fractured if the ratio of the central vertebral height to the anterior or posterior vertebral body height was less than 0.8, or the ratio of the anterior to the posterior vertebral body height was less than 0.75, or the anterior, central, and posterior vertebral heights were decreased by more than 20% compared with those of the adjacent vertebral body. Investigators assessed non-vertebral fractures, withdrawals due to adverse events, and gastrointestinal adverse events as adverse events, but did not provide sufficient information about assessment methods.
Notes	Funded by a grant from the Joint Development Program of Ajinomoto Co., Inc., Aventis Pharma Ltd, and Takeda Chemical Industries Ltd. Two male participants were included in the risedronate group despite not meeting our predefined inclusion criteria.

Fukunaga 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The eligible patients were randomly assigned to receive either..." A method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	A method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Low risk	"The study masking was maintained by a double-dummy technique using two kinds of placebos of risedronate and etidronate. The active drug and placebo were indistinguishable from each other." We judged the blinding methods to be appropriate for blinding participants and personnel.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	We judged the blinding methods to be appropriate for blinding participants and objective outcome assessors.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	We judged the blinding methods to be appropriate for blinding participants and subjective outcome assessors.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"There was no significant difference between the two treatment groups with regard to the proportion of patients who completed the study, or who were withdrawn from the study." The completion rates in the risedronate and etidronate groups were 83% and 87%, respectively. All fractures except for vertebral fractures were recorded as safety outcomes. For vertebral fractures, 101 and 111 participants in the risedronate and etidronate group were assessed, respectively. For non-vertebral, hip, and wrist fractures, all randomized participants were included. We judged the study to be at low risk of bias given that the overall completion rate exceeded 80%, and the numbers of and reasons for discontinuations in each group appeared balanced.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	"There was no significant difference between the two treatment groups with regard to the proportion of patients who completed the study, or who were withdrawn from the study." All randomized participants were included, with completion rates of 83% and 87% in the risedronate and etidronate groups, respectively. We judged the study to be at low risk of bias given that the overall completion rate exceeded 80%, and the numbers of and reasons for discontinuations in each group appeared balanced.
Selective reporting (reporting bias)	Low risk	Protocol was not available. We judged the study to be at low risk of bias given that all the outcomes prespecified in the method section were also reported in the results section.
Other bias	Low risk	Two male participants were included in the risedronate group despite not meeting our predefined inclusion criteria. While acknowledging that the extracted data might have been affected, we judged the influence to be minimal, given it was a small percentage (2/235, 0.9%) of the total population.

Guañabens 2000

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: three years Blinding: NR, but the film observer appeared to be blinded Trial completion: 78/118 (66%) • Etidronate: 47/63 (75%) • Sodium fluoride: 31/55 (56%)
Participants	Inclusion criteria: women with established postmenopausal osteoporosis (mean lumbar BMD -3.2 SD below the young adult mean and one or more non-traumatic vertebral fractures). Exclusion criteria: previous hip fracture, associated disease or treatment known to induce osteoporosis, and impaired renal function. None of the patients had a history of taking bisphosphonates or fluoride. Age: 64.5 (6.9) years Time since menopause: 18.1 (19.5) years Mean BMI: 26.7 (0.8) kg/m^2 Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: -3.3 (0.2) Femoral neck T-score: -2.8 (0.1) Prevalent vertebral fracture: 118 (100%) Previous bisphosphonate experience: 0% Source: Spain, three centres Race/ethnicity: NR
Interventions	Two-arm comparison: • Etidronate 400 mg/day for 14 days, followed by calcium 1 g/day for 76 days • Sodium fluoride 50 mg/day (25 mg, twice daily) and calcium 1 g/day
Outcomes	Radiographic vertebral fractures: lateral X-ray films of the thoracic and lumbar spine were obtained at entry and yearly for up to 3 years, and were evaluated by two independent observers. Vertebral fracture was defined as a reduction of ≥ 20% in the anterior, middle, or posterior height of the vertebral body. Re-fracture was considered to have occurred if any of the 3 vertebral heights had decreased by ≥ 15% in a previously fractured vertebra. Non-vertebral fractures: non-vertebral fractures were recorded every 6 months. In case of lower extremity pain syndrome, an X-ray film of the painful area and a bone scan were performed. The above fracture outcomes appeared to be assessed and reported as efficacy outcomes. Investigators assessed two safety outcomes, withdrawals due to adverse events and gastrointestinal adverse events, but did not provide sufficient information about assessment methods.

Guañabens 2000 *(Continued)*

Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"…patients were randomly assigned to receive…" Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and blinding approach was not provided. It was likely open-label because two treatments had different dose schedules: intermittent cyclic versus continuous daily use of the drugs.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"The films were evaluated by two independent observers who did not know the patient's treatment group. Vertebral fracture was defined as a reduction of 20%..." Blinding of participants was not mentioned and blinding approach was not provided. However, vertebral fracture assessment was conducted by independent observers with radiographic evidence and objective criteria. Ascertainment of other fracture outcomes was also conducted as needed.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Blinding was not mentioned and blinding approach was not provided. Judged to be at high risk of bias given that the subjective outcomes might be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment if the blinding was not conducted or ineffective.
Incomplete outcome data (attrition bias) Efficacy outcomes	High risk	"Analyses of BMD, fracture data, and adverse effects, were performed only on the patients who completed the 3 year study... Thirty-one patients in the fluoride group and 47 in the etidronate group completed the 3 year trial." Fracture outcomes appeared to be assessed and reported as efficacy outcomes. Not all randomized participants were included in the analysis. Seventy-five percent (47/63) and 56% (31/55) of participants in the cyclic etidronate and sodium fluoride group completed the 3-year study, respectively. Judged to be at high risk of bias given that both of the completion rates were less than 80% and the approach to handling missing data was not provided.
Incomplete outcome data (attrition bias) Safety outcomes	High risk	Two safety outcomes, withdrawals due to adverse events and gastrointestinal adverse events, were reported. Only the participants who completed the study were included and the approach to handling missing data was not provided for the high early discontinuations. In addition, the rate of withdrawals due to adverse events was 3/63 (4.8%) in the etidronate group, and 13/55 (23.6%) in the fluoride group, which were very different across groups.
Selective reporting (reporting bias)	Low risk	Protocol was not available. Judged to be at low risk of bias, as all the outcomes prespecified in the methods section were also reported in the results section.
Other bias	Low risk	None were identified.

Gürlek 1997

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: one year Blinding: NR Trial completion: 30/30 (100%) • Etidronate + calcitriol 0.5 µg/day: 10/10 (100%) • Calcitonin + calcitriol 0.25 µg/day: 10/10 (100%) • Calcitriol 0.5 µg/day: 10/10 (100%)
Participants	Inclusion criteria: postmenopausal women aged 45 to 68 referred to outpatient clinic because of a clinical diagnosis of osteoporosis. The menopause was determined by clinical history, and was defined as an absence of menses for at least one year. The diagnosis of osteoporosis was based on the presence of one or more nontraumatic vertebral compression fractures and demineralisation of vertebrae as seen on a lateral spinal roentgenogram; a fracture was defined as a reduction in the height of the anterior border of a vertebral body by 15% or more, as compared with the height of the posterior border. All participants were white, were taking no medications for treatment of osteoporosis, and were ambulatory. All had normal results from tests for serum electrolytes, glucose, calcium, phosphate, alkaline phosphatase, liver function, creatinine, thyroid function, protein electrophoresis, urinalysis, haematocrit, and leukocyte count. All participants were nonsmokers. Exclusion criteria: history of corticosteroids, anticonvulsant, or oestrogen use, malnutrition, alcohol intake, sarcoidosis, liver disease, rheumatoid arthritis, nephrolithiasis, renal disease, or malignancy were excluded. Age: 55.7 (1.1) years Time since menopause: 9.4 (5.5) years BMI: NR Lumbar spine BMD: 0.85 (0.03) g/cm^2 Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: 0% Source: Turkey Race/ethnicity: Caucasian (100%)
Interventions	Three-arm comparison: • Etidronate + calcitriol: etidronate 400 mg/day for 14 days then calcitriol 0.25 µg twice daily for 60 days for 5 cycles • Calcitonin + calcitriol: salmon calcitonin 100 IU, IN, every second day plus calcitriol 0.25 µg daily • Calcitriol 0.25 µg twice daily All participants received daily calcium 500 mg nightly.
Outcomes	No fracture outcomes of interest were reported.

Gürlek 1997 *(Continued)*

	Data for withdrawals due to adverse events were inferred as zero, as all participants completed the trial.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomly assigned by computer to three treatment groups."
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	No information was provided about blinding. It looked like an open-label study due to the distinct treatments. For example, calcitriol was taken twice daily in groups 1 and 2, but every other day in group 3. Calcitonin was administered via intranasal device and there was no mention of placebo. It was likely the participants and personnel were not blinded at all.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	No information was provided about blinding. It looked like an open-label study due to the distinct treatments. For example, calcitriol was taken twice daily in groups 1 and 2, but every other day in group 3. Calcitonin was administered via intranasal device and there was no mention of placebo. The assessment of subjective outcomes was subject to a high risk of bias in an open-label trial.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	"All women enrolled in the study completed the one-year treatment program." Only the outcome of withdrawals due to adverse events was reported. The completion rate was 100% with no missing data.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes appear to have been reported as described in the methods section.
Other bias	Low risk	It appeared to be free of other risks of bias.

Hasling 1994

Study characteristics

Methods	Randomized, active-controlled trial Secondary prevention Duration: 3 years Blinding: NR Trial completion: 45/74 (61%) • Etidronate: 16/19 (84%) • ADFR: 6/18 (33%) • Calcium: 9/17 (53%) • HRT: 14/20 (70%)

Hasling 1994 *(Continued)*

Participants	Inclusion criteria: women aged 52 to 75 years with symptomatic spinal osteoporosis and who had at least 1 and a maximum of 4 (mean 3.4) low-energy spinal fractures. They were a minimum of 2 years postmenopausal. Exclusion criteria: older than 75 years, receiving drugs with a known influence on bone or calcium metabolism, a history of excess alcohol intake or abnormal thyroid, liver or renal function. Age: 66.5 (4.8) years Time since menopause: 19.1(8.0) years BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: 0% Source: Denmark Race/ethnicity: NR
Interventions	Four-arm comparison: • Etidronate: 400 mg daily for 2 weeks followed by 13 weeks without etidronate for 10 cycles • ADFR: a cycle started with triiodothyronine (T3) 50 µg twice daily for 1 week, followed by 400 mg etidronate disodium daily for another 2 weeks, and then 12 weeks off treatment. 10 cycles were repeated. • Calcium: elemental calcium (Mega-calcium, Sandoz) 2000 mg/day in two divided doses • HRT: cyclical oestrogen/progestogen (Trisequens, Novo) consisting of 2 mg oestradiol and 1 mg oestriol daily from day 1 through day 12; 2 mg oestradiol, 1 mg oestriol, and 1 mg norethisterone acetate daily from day 13 through day 22; and 1 mg oestradiol and 0.5 mg oestriol from day 23 through day 28. The cycle was then repeated. All participants received a daily multivitamin tablet containing 400 IU vitamin D_3. In addition, groups 1, 2, and 4 received 120 mg elemental calcium daily as calcium phosphate.
Outcomes	Radiographic vertebral and non-vertebral fractures were narratively described without providing the numbers of participants sustaining the fractures. Dropouts were reported as "drug-related" without further definition. We do not know if there were any withdrawals due to adverse events which were not related to the intervention drugs. Data related to withdrawals due to adverse events were not usable.
Notes	Funding information: "The study was supported in part by a grant from the Danish Medical Research Council (grant no. 12-6175), and grants from the P. Carl Pedersen Foundation, the University of Aarhus Research Foundation, and the Institute of Clinical Experimental Research at the University of Aarhus, Denmark. Procter & Gamble Pharmaceuticals, Norwich, New York, supplied the etidronate and provided financial support for investigating groups 1, 2 and 3 and the first 12 patients of group 4; Novo Pharmaceuticals A/S, Gentofte, Denmark, supported the study financially and supplied the oestrogen/progestogen preparations (Trisequens). Sandoz AG, Basel, Switzerland, supplied the Megacalcium Sandoz preparations." No outcome data of interest were extracted. We did not include this study in quantitative synthesis.
Risk of bias	

Hasling 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomized to four different treatment groups" The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Selective reporting (reporting bias)	Low risk	Protocol was not available. However, the reported outcomes appeared to have been pre-planned in the methods section.
Other bias	Low risk	This study appeared to be free of other risks of bias.

Heath 2000

Study characteristics	
Methods	Randomized controlled trial Primary prevention Duration: 2 years Blinding: open-label Trial completion: 55/77 (71%) • Etidronate: 22/38 (58%) • Control: 33/39 (85%)
Participants	Inclusion criteria: ambulatory, active postmenopausal women over 40 years of age with a body weight of between 45 and 90 kg who had ceased menstruating between 6 and 36 months prior to enrolment. Exclusion criteria: history of alcoholism; significant psychiatric, endocrine, gastrointestinal, hepatic, cardiac, or renal disease; malignancy, or metabolic bone disease, including a history of fragility fracture. Other exclusion criteria were previous treatment with bone active drugs such as glucocorticoids, anabolic agents, calcitonin, hormone replacement therapy, vitamin D (at doses > 400 IU daily) or calcium (at doses > 500 mg daily) within the previous 6 months, and bisphosphonate therapy within the previous 12 months. Women with marked menopausal symptoms or suspected vitamin D deficiency were also excluded. Age: 52.5 (3.6) years Time since menopause: 2.1 (1.1) years BMI: NR Lumbar spine BMD (SD) 1.16 (0.14) g/cm^2 Femoral neck BMD: 0.91 (0.11) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 0% Previous bisphosphonate experience: NR Source: UK, one centre

Heath 2000 *(Continued)*

	Race/ethnicity: NR
Interventions	Two-arm comparison: • Etidronate 400 mg/day for 14 days, followed by 76 days of calcium supplementation (500 mg elemental calcium daily). The 90-day treatment cycle was repeated for 2 years. • Control: no treatment
Outcomes	None of the fracture outcomes of interest were reported. Gastrointestinal adverse events, serious adverse events, withdrawals due to adverse events: women were questioned about suspected adverse events at each visit after the start of treatment. These included any undesirable clinical experience, any suspected adverse reaction, and any exacerbation of a pre-existing condition. A serious adverse event was defined as death, cancer, overdose, life-threatening or permanently disabling events, and events requiring or extending hospitalization. Gastrointestinal events included nausea or dyspepsia, and this outcome was extracted as number of events.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"This was an open, randomized controlled study in which women were randomly assigned to treatment..." No detailed methods were mentioned.
Allocation concealment (selection bias)	Unclear risk	No detailed methods were mentioned.
Blinding of participants and personnel (performance bias)	High risk	"This was an open, randomized controlled study in which women were randomly assigned to treatment..." Open-label study, in which participants and personnel were not blinded and performance bias was less likely to be prevented.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"This was an open, randomized controlled study in which women were randomly assigned to treatment..." Open-label study: we judged that assessment of subjective safety outcomes was at high risk of detection bias.
Incomplete outcome data (attrition bias) Safety outcomes	High risk	"Fifty-five subjects completed 104 wk on the study. Of those who withdrew, 6 were in the control group and 16 in the treatment group. Reasons for withdrawal were as follows: adverse event (1 control, 7 etidronate), poor compliance (2 in the treatment group), lost to follow-up or subject did not wish to continue (3 control and 6 etidronate), and commencement of hormone replacement therapy (2 control, 1 etidronate)." Three safety outcomes - withdrawals due to adverse events, serious adverse events, and gastrointestinal adverse events - were extracted. For withdrawals due to adverse events, all withdrawals were accounted for and judged to be at low risk of bias. However, for the latter two, the unbalanced completion rates (treatment group 42% versus 15.4% in control group) and lack of approach for handling missing data made the outcome data subject to high risk of bias.
Selective reporting (reporting bias)	Low risk	Safety outcomes were mentioned in the methods section and reported in the results section. The other reported outcomes appear to have been reported as pre-planned in the methods section.

Heath 2000 *(Continued)*

Other bias	Low risk	It appeared to be free of other risks of bias.

Herd 1997

Study characteristics	
Methods	Randomized, placebo-controlled trial Primary prevention Duration: 2 years Blinding: double-blind Trial completion: 135/152 (89%) • Etidronate: 64/75 (85%) • Placebo: 71/77 (92%)
Participants	Inclusion criteria: white, ambulatory, 1 to 10 years postmenopausal (FSH confirmed > 50 IU). T-score of 0 to -2 SD of normal values for a 50-year-old woman measured in local population (dual photon absorptiometry of spine, hip, and total body were measured). Exclusion criteria: prevalent vertebral, hip, or wrist fracture unrelated to severe trauma, hyperparathyroidism or bone disease, cancer within the last 5 years except epitheliomas of the skin, significant psychiatric or organic disease, any laboratory abnormalities; treatment with corticosteroids, anabolic drugs, calcitonin, vitamin D (at doses exceeding 400 units/day), oestrogens and/or progestogens within 6 months prior to recruitment; or previous treatment with fluoride or any bisphosphonate. Age: 54.8 (5.0) years Time since menopause: 5.5 (2.9) years BMI: NR Lumbar spine BMD: 0.84 (0.8) g/cm^2 Femoral neck BMD:0.70 (0.09) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 0% Previous bisphosphonate experience: 0% Source: UK Race/ethnicity: white (100%)
Interventions	Two-arm comparison: • Etidronate 400mg/day for 14 days, followed by calcium 500 mg/day for 76 days • Placebo for 14 days, followed by calcium 500 mg/day for 76 days Each 90-day cycle was repeated 8 times over 2 years.
Outcomes	Radiographic vertebral fractures: lateral radiographs of thoracic and lumbar spine at baseline and 24 months. This outcome appears to have been reported as an efficacy outcome. Three safety outcomes of interest were reported. At each visit (6, 12, 18, 24 months), clinical evaluation of the women was performed. A serious adverse event was defined as death, overdose, a diagnosis of

Herd 1997 *(Continued)*

	cancer, or any event that was life-threatening. Gastrointestinal adverse events included nausea, dyspepsia, and diarrhoea. Details were not reported for withdrawals due to adverse events.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"This was a single-center, outpatient, randomized… Subjects were stratified into one of three strata according to years since the menopause (1 to 3 years, 4 to 6 years and 7 to 10 years), and then randomly allocated to one of two groups." Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"This was a single-center, outpatient, randomized, double-blind, placebo-controlled trial." Blinding approach was not provided and it was not clear if the blinding was effective to prevent the participants and the personnel from knowing the assigned treatments.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"This was a single-center, outpatient, randomized, double-blind, placebo-controlled trial." Blinding approach was not provided but we judged that the study was at low risk of bias in the assessment of objective outcomes, which were based on rigorous clinical criteria and less likely to be biased.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	As above: blinding approach was not provided. We judged the study to be at unclear risk of bias because the reporting and assessment of subjective outcomes could be influenced by the participants' or assessors' knowledge of the allocated interventions if blinding was ineffective.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"All analyses presented were performed for the intent-to-treat population (all subjects who were randomized to treatment)." All the randomized participants were included in the analysis, with a 2-year completion rate of 89% (135/152). The numbers and reasons for discontinuation in the two groups seem balanced, except that 5 participants withdrew from the study for adverse events, but none of these were in the placebo group. No methods were provided for handling missing data. We judged the study to be at low risk of bias given that the overall completion rate was high and the unreported missing data seemed unlikely to bias the outcome estimate.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	As above: all the randomized participants were included in the analysis, with a 2-year completion rate of 89% (135/152). For the outcome of withdrawals due to adverse events, all withdrawals were reported and all participants were accounted for. In addition, for serious adverse events and gastrointestinal adverse events, the risk of bias was also judged to be low, given the low attrition, which would less likely impact the estimate of the effect size.
Selective reporting (reporting bias)	Low risk	Protocol was not available. However, all outcomes were prespecified in the methods section and reported in the results section.
Other bias	Low risk	None were identified.

Hu 2005

Study characteristics	
Methods	Randomized controlled trial Secondary prevention Duration: 12 months Blinding: NR Trial completion: NR/150 (excluding one group of 38 postmenopausal women at lower risk of fractures who were not randomized.) • Etidronate: NR/50 • HRT: NR/50 • Control: NR/50
Participants	Inclusion criteria: postmenopausal women aged more than 45 years old with menopause duration of 1 to 27 years; body mass index (BMI) 15.24 to 38.58 kg/m^2; and in accordance with the 1994 WHO diagnostic criteria (BMD results lower than 2.5 SD of the normal same-sex peak value, and not caused by disorders); gave informed consent. Exclusion criteria: comorbidity with severe malnutrition, severe liver and kidney impairments or disorders of the uterus and milk glands. Age: NR Time since menopause: NR BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: NR Previous bisphosphonate experience: NR Source: China, one hospital Race/ethnicity: Asian (100%)
Interventions	Three-arm comparison: • Etidronate: each cycle contained etidronate 200 mg twice a day for 2 weeks, followed by 11 weeks of no treatment. The treatment cycle was repeated for 12 months. • HRT: Livial 1 tablet/day, containing tibolone 2.5 mg • Control: Caltrate 1 tablet/day, containing calcium 600 mg and vitamin D3 125 IU
Outcomes	This study reported the quality of life (QoL) outcome. However, the QoL total scores were only available post-treatment (12 months), with an apparent error in one group's score. Due to the absence of QoL total scores at baseline, we could not establish the change scores (from baseline) for QoL in each group.
Notes	Funded by National "Tenth Five-Year" Science and Technology Project (2001BA702B04) We extracted no outcome data of interest to the review, and did not include this study in the quantitative synthesis.

Hu 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Except for 38 patients in the control group who had health issues (eg., no history of fracture, mild symptoms, etc.), the remaining 150 patients were entirely randomized to..." The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes appeared to be reported as pre-specified in the method section.
Other bias	High risk	The publication is in Chinese with an English abstract. The comparator drug "邦得林" was found to be "etidronate" but not as reported "risedronate'. In addition, the QoL total score for the HRT group was apparently incorrect. It was judged to be at high risk of bias in this domain given the serious faults.

Ishida 2004

Study characteristics

Methods	Randomized, active-controlled trial Secondary prevention Duration: 2 years Blinding: NR, but "All endpoints were evaluated by independent physicians in a blinded endpoint committee." Trial completion: 372/396 (96%) • Etidronate: 62/66 (94%) • HRT: 62/66 (94%) • Calcitonin: 62/66 (94%) • Alfacalcidol: 63/66 (95%) • Menatetrenone: 63/66 (95%) • Control: 60/66 (91%)
Participants	Inclusion criteria: ambulatory women aged 50 to 75; at least 5 years since natural or surgical menopause. Osteoporosis was defined as 1 or more vertebral fractures plus BMD at least 20% below young adult mean (-2.5 distal radius T-score), or BMD at least 30% (-3.5) below young adult mean alone. Exclusion criteria: recent cancer, metabolic bone disease, recent use of drugs affecting bone metabolism, history of bilateral hip fractures, important abnormalities in routine laboratory tests, or any physical or mental condition that would preclude participation. Age: 69.3 (13.3) years Time since menopause: 19.8 (NR) years BMI: NR Lumbar spine BMD: NR

Ishida 2004 *(Continued)*

	Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 30% Previous bisphosphonate experience: NR Source: Japan, one hospital Race/ethnicity: Asian (100%)
Interventions	Six-arm comparison: • Etidronate 200 mg/day for 2 weeks, followed by 10-week medication-free periods • HRT: conjugated oestrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day • Calcitonin: intermittently eel calcitonin 20 IU/week, IV (route used in Japan) • Alfacalcidol 1 µg/day • Menatetrenone (vitamin K_2) 45 mg/day • Control: no treatment
Outcomes	Radiographic vertebral fractures: lateral thoracic and lumbar spine radiographs at baseline and 3-month intervals. Incident fractures diagnosed quantitatively (a decrease of at least 20% for intact vertebrae at baseline or at least 4 mm for fractured vertebrae at baseline) and semi-quantitatively (vertebrae were scored as 0 for none, 1 for mild, 2 for moderate, and 3 for severe fractures. An incident fracture was defined as a grade change of at least 1). Investigators assessed non-vertebral, hip and wrist fractures, but provided insufficient information about assessment methods. Withdrawals due to adverse event: reported as "adverse events" as reasons for discontinuation. No further information was provided.
Notes	Funding information: NR Study name: the Yamaguchi Osteoporosis Prevention Study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"…according to a dynamic balancing method (modified minimization method) using two balancing factors (age, baseline prevalence of vertebral fracture)."
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and no approach was described for preventing participants and personnel from knowing the assigned treatments. It was likely open-label because six arms involved different dose schedules and routes, in which the performance of the participants and personnel was likely influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"All endpoints were evaluated by independent physicians in a blinded endpoint committee... Lateral thoracic and lumbar spine radiographs were obtained at baseline and at 3-month intervals. Prevalent (baseline) and incident (new) vertebral fractures were diagnosed quantitatively and semiquantitatively."

Ishida 2004 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	As above, only the outcomes assessors were blinded; the participants were likely not blinded. The reporting and assessment of subjective outcomes might have been influenced by the participants' knowledge of the allocated interventions if blinding was not conducted. Judged to be at high risk of bias.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"The secondary efficacy measure was the incidence of vertebral fractures... Results were analyzed on an intention-to-treat basis." The overall 2-year completion rate was 94% (372/396), ranging from 90% to 95%. The bias from the missing data was expected to be minor. Judged to be low risk of bias.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	The statistical plan for safety outcomes was not provided. However, as above, the completion rates were quite high across groups and the bias from the missing data was expected minor. It was judged to be at low risk of bias.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available, but the outcomes of interest were reported as described in the methods section. However, there seemed to be no monitoring or reporting of safety outcomes, except for withdrawals due to adverse events, which does not meet standard reporting practices of clinical trials.
Other bias	High risk	None was identified. However, study author Yoichiro Ishida seems to have been involved in a retraction issue (https://retractionwatch.com/2020/07/02/an-influential-osteoporosis-study-is-likely-fraudulent-but-not-retracted). Study might be subject to other risks of bias.

Iwamoto 2001

Study characteristics	
Methods	Randomized, active controlled trial Secondary prevention Duration: 24 months Blinding: open-label Trial completion: NR/72 • Etidronate: NR/25 • Menatetrenone: NR/23 • Control: NR/24
Participants	Inclusion criteria: women who were 53 to 78 years of age, more than 5 years after menopause, who were diagnosed as having osteoporosis by Japanese criteria. Exclusion criteria: had a history of hormone (oestrogen) replacement therapy, had ever taken medication that affects bone metabolism prior to the present trial, had participated in sporting activity for at least the previous 5 years and was involved in such activity during the trial, or had levels of serum calcium, phosphorus, and alkaline phosphatase outside the normal limits. Age: 65.2 (1.2) years Time since menopause: 17.1 (1.3) years BMI: 20.9 (0.7) years Lumbar spine BMD: NR Femoral neck BMD: NR

Iwamoto 2001 *(Continued)*

	Lumbar spine T score: NR Femoral neck T score: NR Prevalent vertebral fracture: 31% Previous bisphosphonate experience: 0% Source: Japan, one hospital Race/ethnicity: Asian (100%)
Interventions	Three-arm comparison: • Etidronate 200 mg/day for 14 days for 3 months • Menatetrenone 45 mg/day • Control: calcium lactate 2 g/day All participants were strictly encouraged to consume 800 mg of calcium and 400 IU of vitamin D daily in their meals, as outlined by the dietitian.
Outcomes	Radiographic vertebral fractures: plain X-ray examination of the thoracic and lumbar spines was obtained to assess the incidence of new vertebral fractures during treatment. The presence of vertebral fracture was confirmed when (1) more than 20% reduction of vertebral height [anterior (A), center (C), and posterior (P)] compared with the neighbouring vertebrae was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75. Investigators assessed non-vertebral, hip and wrist fractures, but did not provide sufficient information about assessment methods. Gastrointestinal adverse events were reported as gastrointestinal symptoms.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly divided into three administration groups…" Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	"…the present open, prospective…" The participants and personnel were not blinded; performance during the study might have been biased.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"Vertebral fracture was defined according to vertebral height obtained from lateral X-ray films, based on the Japanese criteria…" Despite being an open-label trial, we judged it to be at low risk of bias given that the assessment of fracture outcomes were based on objective evidence and were not subject to unblinding risk.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	As above, but we judged it to be at high risk of bias given that the assessment of subjective outcomes would likely be influenced by the participants' or assessors' knowledge of the allocated interventions if blinding was not preformed.

Iwamoto 2001 *(Continued)*

Incomplete outcome data (attrition bias) Efficacy outcomes	Unclear risk	In this 2-year study, the analysis plan and attrition information were not reported. We judged it to have an unclear risk of bias given the limited information.
Incomplete outcome data (attrition bias) Safety outcomes	Unclear risk	As above: judged to have an unclear risk of bias given the limited information.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as described in the methods section.
Other bias	High risk	None was identified. However, the study author Jun Iwamoto seems to have been involved in a retraction issue (https://retractionwatch.com/2020/07/02/an-influential-osteoporosis-study-is-likely-fraudulent-but-not-retracted). Study might be subject to other risk of bias.

Iwamoto 2003b

Study characteristics	
Methods	Randomized, placebo-controlled trial Secondary prevention Duration: 12 months Blinding: open-label Trial completion: 40/40 (100%) • Etidronate: 20/20 (100%) • Etidronate + alfacalcidol: 20/20 (100%)
Participants	Inclusion criteria: "postmenopausal women 60 to 86 years of age with no vertebral fractures in the lumbar spine were recruited at our hospital between January and March 2001. All of them were diagnosed as having osteoporosis based on Japanese criteria." Exclusion criteria: NR Age: 71.2 (6.2) years Time since menopause: 21.1 (6.2) years BMI: 21.3 (3.1) kg/m^2 Lumbar spine BMD: 0.59 (0.10) g/cm^2 Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 0% Previous bisphosphonate experience: 0% Source: Japan Race/ethnicity: Asian (100%)
Interventions	Two-arm comparison:

Iwamoto 2003b *(Continued)*

- Etidronate 200 mg/day for 2 weeks every 3 months
- Etidronate 200 mg/day for 2 weeks every 3 months and alfacalcidol 1 µg/day, continuously

(Calcium 800 mg/day was given to all the participants throughout the study.)

Outcomes	Radiographic vertebral fractures: radiographs of the thoracic and lumbar spine were obtained, and vertebral fracture was defined according to the vertebral height obtained from lateral radiographs based on Japanese criteria: vertebral height was measured at the anterior (A), center (C), and posterior (P) parts of the vertebral body; the presence of a vertebral fracture was confirmed when (1) there was more than a 20% reduction of vertebral height (A, C, P) compared with the neighbouring vertebrae; (2) the C/A or C/P ratio was less than 0.8; or (3) the A/P ratio was less than 0.75. Assessment of vertebral fractures was performed for the T4–L4. The study reported zero events in both groups for the outcomes: hip and wrist fractures, withdrawals due to adverse events, and gastrointestinal adverse events, but it did not provide sufficient information about assessment methods.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The purpose of the present open-labelled, randomized, prospective study was to compare..." The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	As above, the method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	The participants and personnel were not blinded; performance was likely to be biased.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"Radiographs of the thoracic and lumbar spine were obtained and vertebral fracture was defined according to the vertebral height obtained from lateral radiographs based on Japanese criteria..." As above, it was an open-label study. However, the fracture outcomes were assessed by clinical evidence, with or without radiographic/morphometric methods, which were less likely to be biased by the lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	For the outcome of gastrointestinal adverse events, assessments were likely to be biased due to the lack of blinding.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"Informed consent was obtained from each of the participants, and all participants completed the present trial. " No early discontinuation occurred and there was no attrition bias.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	As above; judged to be at low risk of bias.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as described in the methods section.
Other bias	High risk	None was identified. However, the study author Jun Iwamoto seems to have been involved in a retraction issue (https://retraction-

Iwamoto 2003b *(Continued)*

	watch.com/2020/07/02/an-influential-osteoporosis-study-is-likely-fraudulent-but-not-retracted). Study might be subject to other risks of bias.

Iwamoto 2005

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: 12 months Blinding: open-label Trial completion: 50/50 (100%) • Etidronate: 25/25 (100%) • Alendronate: 25/25 (100%)
Participants	Inclusion criteria: postmenopausal women 55 to 86 years old who were diagnosed as having osteoporosis according to the Japanese criteria (patient's BMD was < 70% of the young adult mean (YAM) or 70% to 80% of the YAM with a history of osteoporotic fractures). Exclusion criteria: past history of reflux oesophagitis, gastric or duodenal ulcer, or gastrectomy; suffered from any metabolic bone disease, had a history of hormone (oestrogen) replacement therapy or had ever taken medication that affects bone metabolism prior to the study. Age: 70.7 (7.3) years Time since menopause: 20.9 (6.8) years BMI: NR Lumbar spine BMD: 0.58 (0.11) g/cm^2 Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Mean number of prevalent vertebral fractures per patient: 2.5 (2.9) Previous bisphosphonate experience: 0% Source: Japan Race/ethnicity: Asian (100%)
Interventions	Two-arm comparison: • Etidronate 200 mg/day for 2 weeks every 3 months • Alendronate 5 mg/day (All participants were instructed to take 800 mg of calcium daily in their food intake during the study.)
Outcomes	Radiographic vertebral fractures: plain X-ray examination of the thoracic and lumbar spines was obtained to assess the incidence of new vertebral fractures during treatment. The presence of vertebral fracture was confirmed when (1) more than 20% reduction of vertebral height [anterior (A), center (C), and posterior (P)] compared with the neighbouring vertebrae was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75 (Japanese criteria).

Iwamoto 2005 *(Continued)*

	We inferred that there were zero withdrawals due to adverse events from the sentence: "all patients who experienced these side effects were able to continue taking the medicine." Investigators assessed non-vertebral, hip and wrist fractures, serious adverse events, and gastrointestinal adverse events but did not provide sufficient information about assessment methods.
Notes	This study was not funded, which we inferred from the text: "We have no funding sources; We have no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"...were randomly divided into two groups with 25 patients in each group... They were divided one by one in the order of recruiting into two groups. the cyclical etidronate (200 mg daily for 2 weeks every 3 months) group and the alendronate (5 mg/daily) group." The method of sequence generation, "one by one in the order of recruiting", was easy for either participant or investigator to guess the assigned treatment. Judged to be at high risk of bias.
Allocation concealment (selection bias)	High risk	The method of allocation concealment was not provided. Given the sequence generation was not ideal, the concealment of treatment allocation would be subject to high risk of bias.
Blinding of participants and personnel (performance bias)	High risk	“The purpose of this open-labelled prospective study…” The participants and the personnel were not blinded and their performances during the study duration were likely influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"The presence of vertebral fracture was confirmed when (1) more than 20% reduction of vertebral height [anterior (A), center (C), and posterior (P)] compared with the neighbouring vertebrae was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75. " Although the trial was open-label, the assessment of objective outcomes, which normally required clinical and/or radiographic evidence to support the occurrence of an incident, was less likely biased.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"Because pain is a subjective symptom, there was difficulty in evaluating back pain using the face scale score." Judged to be at high risk of bias given that the assessment of subjective outcomes would likely have been influenced by the participants' and assessors' knowledge of the allocated interventions if blinding was not performed.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	In this 12-month trial, all the randomized participants completed the study and were included in the analysis. Judged to be at low risk of bias.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	As above: judged to be at low risk of bias for other safety outcomes of interest.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as pre-specified in the method section.

Iwamoto 2005 *(Continued)*

Other bias	High risk	It appeared to be free of other risks of bias. However, we judged it to be at high risk of bias given that the first author, Jun Iwamoto, has been involved in, and scrutinized for, a study retraction event.

Köşüş 2005

Study characteristics	
Methods	Randomized controlled trial Secondary prevention Duration: 1 year Blinding: open-label Trial completion: 59/70 (84%) • Cyclic etidronate: 18/22 (82%) • Alendronate 10 mg/day: 20/24 (83%) • Cyclic alendronate 10 mg/day: 21/24 (88%)
Participants	Inclusion criteria: women older than 45 years and postmenopausal for a minimum of 2 years, who were diagnosed with primary osteoporosis because their BMD values were lower than 2.5 standard deviations below normal. Exclusion criteria: had secondary causes of osteoporosis Age: 50 (NR) years Time since menopause: 5.3 (NR) years BMI: NR Lumbar spine BMD: 0.70 (NR) g/cm^2 Femoral neck BMD: 0.63 (NR) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures at baseline: NR Previous bisphosphonate experience: NR Source: one site in Turkey Race/ethnicity: NR
Interventions	Three-arm comparison: • Alendronate 10 mg/day • Cyclic etidronate 400 mg/day: etidronate 400 mg/day for 14 days followed by 76 days of calcium tablets. The cycle was repeated for one year. • Cyclic alendronate 10 mg/day: alendronate sodium 10 mg/day for 14 days, followed by 76 days of calcium tablets. The cycle was repeated for one year.
Outcomes	None of the fracture outcomes of interest were reported.

Köşüş 2005 *(Continued)*

	Investigators assessed withdrawals due to adverse events but did not provide sufficient information about assessment methods.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...70 remaining women with osteoporosis and written informed consent as obtained from all. The women were then randomly assigned to 3 groups." The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned; it was very likely to be an open-label study due to three different dose schedules (continuously versus cyclic) and different drugs. Judged to be at high risk of bias given that blinding of participants and personnel appeared infeasible.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	The lack of blinding for participants and assessors would likely influence their reporting and assessment of the subjective outcomes.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	The reporting of safety outcomes was rather brief and inconclusive. Only withdrawals due to gastrointestinal complications were reported. However, the overall completion rate was 84%, so we deemed the amount of missing info was unlikely to influence the estimate of effect size. Judged to be at low risk of bias.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. The reporting of the study was rather simple, and it was not clear if the reported outcome items matched what was pre-specified. There seemed to be no monitoring and reporting of any safety outcome or adverse events, which does not meet standard reporting practices of clinical trials.
Other bias	Unclear risk	The study was presented as a brief communication. The information provided was insufficient and might be subject to bias.

Lyritis 1997

Study characteristics

Methods	Randomized, controlled trial Secondary prevention Duration: 4 years Blinding: open-label Trial completion: 74/100 (74%) • Etidronate: 39/50 (78%) • Control: 35/50 (70%)

Lyritis 1997 *(Continued)*

Participants	Inclusion criteria: osteoporotic women aged 67 to 77 with at least one non-traumatic vertebral collapse, low bone mass density (more than 2 SD below the peak bone mass) and normal biochemical bone markers. Exclusion criteria: bone-acting drugs 1 year prior; secondary osteoporosis Age: 72.0 (0.4) years Time since menopause: 25.8 (1.7) years BMI: NR Lumbar spine BMD (SD): 0.57 (0.03) g/cm^2 Femoral neck BMD: 0.42 (0.03) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: NR Source: Greece, an osteoporosis clinic Race/ethnicity: NR
Interventions	Two-arm comparison: • Etidronate: 1,25-dihydroxyvitamin D3 2 µg/day for 5 days, followed by etidronate 400 mg/day and calcium 500 mg/day for 20 days, and then calcium 500 mg/day for the next 65 days. • Control: 1,25-dihydroxyvitamin D3 2 µg/day for 5 days, followed by calcium 500 mg/day for 85 days. The above followed the ADFR regimen (activation, depression, treatment-free, repeat).
Outcomes	Radiographic vertebral fractures: "lateral radiographs of dorsolumbar spine. The vertebral deformity score was evaluated with use of a semi-quantitative method: (0 (no fracture) 1 (mild - 20-25% reduction in anterior, middle or posterior height accompanied by an area reduction of 10-20%), 2 (moderate - 25-40% reduction in height, 20-40% reduction in area) and 3 (severe - reduction of 40% in height and area)." Non-vertebral, hip, wrist, clinical vertebral and atypical femoral fractures: all fractures of the appendicular skeleton recorded by two independent observers. Withdrawals due to adverse events and serious adverse events: zero events inferred from the text.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"…were enrolled at random…" Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	"…open label cohort study…" The participants and personnel were not blinded, and two treatments were easily distinguished due to different dose schedules. The performance of participants and personnel was likely influenced.

Lyritis 1997 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"All patients had a lateral radiograph of the dorsolumbar spine for the evaluation of vertebral deformities and all fractures of the appendicular skeleton were recorded during the 4-year observation period by two individual observers. The vertebral deformity score was evaluated with use of a semi-quantitative method" Blinding was not performed in this study. However, we judged it to be at low risk of bias given that the objective outcomes were based on clinical and/or radiographic evidence, which was less likely to be influenced by the lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	It was an open-label study, in which the assessment of subjective outcomes of interest would likely be influenced by the participants' or assessors' knowledge of the allocated interventions. Judged to be at high risk of bias.
Incomplete outcome data (attrition bias) Efficacy outcomes	High risk	"Of the 100 patients, 26 discontinued treatment (5 during the first year, 8 during the second, 5 during the third and 8 during the fourth), 11 from the etidronate group and 15 from the non-etidronate group." This was 4-year study, with 95% (95/100), 87% (87/100), 82% (82/100). and 74% (74/100) of the randomized participants completing the study at the first, second, third and fourth year, respectively. The statistical approach was not provided. At the fourth year, 70% of the non-etidronate group and 78% of the etidronate group completed the study. Judged to be at high risk of bias given that the efficacy data were extracted from the fourth year when the completion rates of two groups were less than 80%; the reasons for discontinuation in each group were not reported (the numbers appeared balanced); and the approach to handling missing data was not provided.
Incomplete outcome data (attrition bias) Safety outcomes	High risk	As above: judged to be at high risk of bias given that the safety data of interest were extracted from the fourth year when the completion rates of two groups were less than 80%; the reasons for discontinuation in each group were not reported (the numbers seemed balanced); and the approach to handling missing data was not provided.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as pre-specified in the method section.
Other bias	Low risk	None was identified.

Masud 1998

Study characteristics	
Methods	Randomized controlled trial Secondary prevention Duration: 12 months Blinding: open-label Trial completion: 47/58 (81%) • Etidronate: 23/28 (82%) • Etidronate + calcitriol: 24/30 (80%)
Participants	Inclusion criteria: "women with either a minimum of one non-traumatic vertebral fracture (defined as a 25% reduction in vertebral height calculated from the anterior, posterior or central heights of adjacent

Masud 1998 *(Continued)*

	vertebrae) or those with a BMD that was one and a half standard deviation below the mean for their age based on the DXA manufacturers database (z score < −1.5). The latter criteria were chosen arbitrarily, based on local treatment guidelines, as the study was started shortly before the World Health Organization (WHO) definitions of osteoporosis were published. Nevertheless, all patients recruited had a t score < −2.5 (BMD more than 2.5 standard deviation below the mean peak bone mass; which is confirmed osteoporosis on WHO criteria) at either the lumbar spine or femoral neck." Exclusion criteria: "Women with malignancy, myeloma, thyroid dysfunction, biochemical evidence of hypo- or hyperparathyroidism, renal or liver impairment, evidence of malabsorption, history of gastrectomy, and those taking any drugs affecting calcium and bone metabolism including corticosteroids, thyroxine, diuretics, calcium and vitamin D supplements, hormone replacement therapy, bisphosphonates, and anticonvulsants." Age: 66.3 (8.3) years Years since menopause: 19.2 (7.9) years BMI: NR Lumbar spine BMD: 0.69 (0.13) g/cm^2 Femoral neck BMD: 0.56 (0.07) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: NR Previous bisphosphonate experience: 0% Source: the UK, an osteoporosis clinic Race/ethnicity: Caucasian (100%)
Interventions	Two-arm comparison: • Etidronate: repeated cycles consisting of oral etidronate 400 mg daily for 14 days followed by calcium carbonate 1.25 g (equivalent to 500 mg of calcium when dispersed in water) daily for 76 days • Etidronate + calcitriol: in addition to the cyclic etidronate, calcitriol 0.5 µg/day was added continuously
Outcomes	None of the fracture outcomes were reported. Investigators described withdrawals (due to adverse events), but did not provide sufficient information about assessment methods.
Notes	Funding help was provided by the City Branch of the National Osteoporosis Society.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Those women satisfying the entry criteria for the study were randomly allocated (sequential random numbers method) to..." The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	"Treatment arms were not blinded and placebo not used..."

Masud 1998 *(Continued)*

		The participants and personnel were not blinded. The treatments were distinguishable due to different uses of drugs. The performance of the participants and personnel was likely biased.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Only one subjective outcome, withdrawals due to adverse events, was reported, which would likely be biased due to the lack of blinding.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	Only one safety outcome, withdrawals due to adverse events, was reported. All the randomized participants of the trial were accounted for and not biased by any attrition.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available but the outcomes of interest were reported as described in the methods section. However, there seemed to be no monitoring or reporting of safety outcomes, except for withdrawals due to adverse events, which does not meet standard reporting practices of clinical trials.
Other bias	Low risk	It appeared to be free of other risks of bias.

Meunier 1997

Study characteristics	
Methods	Randomized, placebo-controlled trial Primary prevention Duration: 2 years (followed by a one-year open-label period, in which all participants received elemental calcium 500 mg/day) Blinding: double-blind Trial completion: 49/54 (91%) • Etidronate: 25/27 (93%) • Placebo: 24/27 (89%)
Participants	Inclusion criteria: "Caucasian, ambulatory, between 45 and 90 kg within 15% of normal BMI, between 6 and 60 months post menopause (confirmed by serum estradiol and FSH), normal BMD (Z score within 2 SD for their age)." Exclusion criteria: "bilateral oophorectomy or hysterectomy, disease affecting bone metabolism, prolonged treatment with calcitonin, Vitamin D >400 IU/day calcium greater than 500 IU/day, corticosteroids, or anabolic steroids in previous 6 months, estrogen, progesterone in past year, any past treatment with bisphosphonate or fluoride." Age: 52.7 (0.5) years Time since menopause: 2.4 (0.2) years BMI: NR Lumbar spine BMD: 0.90 (0.02) g/cm^2 Femoral neck BMD: 0.73 (0.02) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: NR

Meunier 1997 *(Continued)*

	Previous bisphosphonate experience: 0% Source: France Race/ethnicity: Caucasian (100%)
Interventions	Two-arm comparison: • Etidronate 400 mg/day for two weeks, followed by calcium 500 mg/day for 11 weeks • Placebo for 2 weeks, followed by calcium 500 mg/day for 11 weeks The above treatments were administered in 90-day cycles over 2 years.
Outcomes	Clinical vertebral and non-vertebral fractures were reported as adverse events, in addition to withdrawals due to adverse events, serious adverse events, and gastrointestinal adverse events. Adverse events were defined as "any undesirable clinical experience occurring to a patient during a study whether related to the investigational drug, which were assessed at each visit from the time the patient received the first dose of the study drug".
Notes	Funded by Procter & Gamble Pharmaceuticals (UK) Limited (one of the six authors was employed by Procter and Gamble).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Twenty seven women were randomized to…" Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Low risk	"…a double-blind, placebo-controlled study.…etidronate and its placebo were identical in appearance." The participants and personnel were appropriately blinded.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"Lateral and anterior/posterior incidence x-rays of the thoracic and lumbar spine were taken at baseline and at 24 months for longitudinal comparison." Multiple methods for blinding participants and outcome assessors were judged effective.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	""…a double-blind, placebo-controlled study.…etidronate and its placebo were identical in appearance." The participants and outcome assessors were appropriately blinded by the approaches. Judged to be at low risk of bias.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"All analyses were performed on the intent-to-treat population (all subjects who were randomized to treatment)." Fracture outcomes were reported as adverse events. This was a 3-year study including 1-year follow-up without treatment. All the randomized participants were included in the study. The 2-year (on-treatment) completion rates were 93% and 89% in the placebo and etidronate groups, respectively. The numbers and reasons for discontinuation in the 2 groups seemed balanced and unrelated to the treatments. Judged to be at low risk of bias given that the overall completion rate was high and the unreported missing data seemed unlikely to bias the outcome estimate.

Meunier 1997 *(Continued)*

Incomplete outcome data (attrition bias) Safety outcomes	Low risk	As above: judged to be at low risk of bias given that the overall completion rate was greater than 80% and the unreported missing data seemed unlikely to significantly bias the safety outcome estimates of interest.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as pre-specified in the method section.
Other bias	Low risk	None were identified.

Montessori 1997

Study characteristics	
Methods	Randomized controlled trial Duration: 3 years. (It was set up as a 2-year trial, but at the end of that time, it was decided to extend the study for another year.) Blinding: open-label Primary prevention Trial completion: 64/80 (80%) • Etidronate: NR/40 • Control: NR/40
Participants	Inclusion criteria: "Postmenopausal for at least 1 year, less than 75 years old, ambulatory, active, with a BMD of the lumbar spine > 1 SD below that of age-matched controls (Z score < -1 SD)." Exclusion criteria: "Systemic treatment with estrogen, androgens, vitamin D, calcium supplementation < 1g/d, calcitonin or bisphosphonates in previous year; suffering from secondary osteoporosis, or other forms of metabolic bone disease, active gastrointestinal or liver disease, renal disease (serum creatinine > 115 µmol/l), active cancer within the last 3 years, or alcoholism." Age: 62.5 (6.2) years Time since menopause: 14.9 (6.1) years Lumbar spine BMD: 0.67 (0.08) g/cm^2 Femoral neck BMD: 0.60 (0.08) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 35% Previous bisphosphonate experience: NR Source: the Netherlands. Race/ethnicity: Caucasian (99%)
Interventions	• Etidronate 400 mg/day for 14 days, followed by calcium 500 mg/day for 76 days (90-day cycles) • Calcium 500 mg/day
Outcomes	Radiographic vertebral fractures: "Posterior-anterior and lateral radiographs of thoracic and lumbar spine performed at entry and every year were evaluated by 2 blinded radiologists. A deformity score was assigned to each individual vertebra as: grade 0, normal; grade 1, 20-25% height loss of the ante-

Montessori 1997 *(Continued)*

	rior, median or posterior aspect of the vertebra in combination with a 10-20% area reduction; grade 2, 25-40% height loss of any aspect of the vertebral body with an area reduction of 20-40%; grade 3, reduction in height and area of > 40%." Hip fractures: investigators provided insufficient information about assessment methods Withdrawals due to adverse events were reported, but information was not conclusive. Zero atypical femoral fractures were inferred from the text.
Notes	Funded by Procter & Gamble Pharmaceuticals, Rotterdam, the Netherlands.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized to two groups by computer in blocks of four." Method was described and likely of low risk.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	"...an open, randomized, controlled prospective trial." The participants and personnel were not blinded; the differences between treatments (etidronate versus calcium) were distinguishable. Their performances were likely influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"The radiographs were displayed on a view box and evaluated by two experienced radiologists from center, who were unaware of the treatment regimen of the patients." It was an open-label trial. However, the assessors for objective outcomes appeared to be blinded, and incidence was based on participants' clinical signs and symptoms.
Incomplete outcome data (attrition bias) Efficacy outcomes	High risk	"Sixty four patients completed 3 years of study; 3 patients discontinued prematurely, all for administrative reasons." Fractures appeared to be reported as efficacy outcomes. Three-year overall completion rate was 64/80 (80%), ranging from 78% in the placebo group to 90% in the etidronate group. The descriptions about the withdrawals due to adverse events were inconsistent. Judged to be at high risk of bias given the completion rate was less than 80% and withdrawals were imbalanced between the two groups.
Incomplete outcome data (attrition bias) Safety outcomes	High risk	The descriptions about the withdrawals due to adverse events were inconsistent. Only one safety outcome, atypical femoral fracture, was extracted. Judged to be at high risk of bias given the completion rate was less than 80% and withdrawals were imbalanced between the two groups.
Selective reporting (reporting bias)	Low risk	Protocol was not available. However, all reported outcomes appeared to be pre-specified in the method section.
Other bias	Unclear risk	Originally, the study was set up as a 2-year trial, but at the end of the study, it was decided to extend the study for another year. It appeared that the extension was not pre-planned and information about the amendment was not provided. Unclear if this change was likely to have led to bias of any kind.

Pacifici 1988

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: two years Blinding: NR Trial completion: 50/128 (39%) • Etidronate + K-phosphate: 16/NR • HRT: 19/NR • Control: 15/NR
Participants	Inclusion criteria: "128 white osteoporotic women who came to our institution for osteoporosis screening. All had at least 1 non-traumatic vertebral fracture and/or evidence of spinal demineralisation by quantitative computed tomography." Exclusion criteria: any condition(s) known to influence calcium metabolism or to contraindicate the medications used in the trial. Age: 60.8 (8.2) years Years since menopause: 13.8 (9.6) years BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: NR Source: the USA, one institution Race/ethnicity: Caucasian (100%)
Interventions	Three-arm comparison: • Etidronate + K-phosphate: K-phosphate 500 mg three times a day for three days, followed by etidronate 200 mg twice a day for 14 days, and then followed by 8 weeks of neither drug. This arm followed the ADFR (activation, depression, treatment-free, repeat) regimen. • HRT: conjugated oestrogens 0.625 mg/day for 25 days per month, and medroxyprogesterone acetate 10 mg/days from days 15-25 each month • Control: no treatment (All participants received calcium 100 mg/day.)
Outcomes	Radiographic vertebral fractures: "Measurements of the vertical height of the anterior, central and posterior regions of each vertebra were made with calipers and a transparent ruler in each lateral spine film. Compression fractures were defined as a loss of posterior height greater than 15% compared with the mean of the posterior height of the nearest (above and below) intact vertebrae. In those vertebrae wherein the posterior height was normal, wedging and biconcave fractures were defined by a loss of anterior and central height greater than 20% compared with the posterior height of the same vertebra." However, reported data were by event and not usable.

Pacifici 1988 *(Continued)*

	None of the safety outcomes of interest were reported.
Notes	Funding information: NR. The only outcome data was reported by (fracture) events instead of number of patients with fracture. This study was not included in the quantitive synthesis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomly assigned to 1 of the 3 treatment groups" The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and no relevant method was provided. It was likely open-label because the three treatments had different drugs and dose schedules. The performance of the participants and personnel were likely influenced if they could distinguish the differences and know the assigned treatments.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"...compression fractures were defined as a loss of posterior height greater than 15% compared with the mean of the posterior height of the nearest (above and below) intact vertebrae. In those vertebrae wherein the posterior height was normal, wedging and biconcave fractures were defined by a loss of anterior and central height greater than 20% compared with the posterior height of the same vertebra." Although this was likely an open-label study, the assessment of objective outcomes was based on clinical and radiographic/morphometric evidence, which was less likely biased.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available, but the outcomes of interest were reported as described in the methods section. However, there seemed to be no monitoring or reporting of safety outcomes, except for withdrawals due to adverse events, which does not meet standard reporting practices of clinical trials.
Other bias	High risk	Study did not provide the numbers of randomized participants in each group and only included the participants who had completed the 1-year treatment in the analysis. In addition, it did not report any safety outcomes. Those uncommon features might have led to a high risk of other bias.

Pouilles 1997

Study characteristics

Methods	Randomized, multicenter, controlled trial Primary prevention Blinding: double-blind Duration: 3 years: 2-year treatment with 1-year follow-up (calcium supplementation only) Trial completion: 91/109 (83%) in two years

Pouilles 1997 *(Continued)*

- Etidronate: 45/54 (83%)
- Control: 46/55 (84%)

Participants	Inclusion criteria: "Caucasian women aged 45- 60 years who were ambulatory and active, weighed between 45 and 80 kg and within 20% of the normal body mass index (BMI), had spontaneously or after bilateral oophorectomy ceased menstruating between 6 and 60 months prior to enrolment and had not been treated by HRT. For those who had ceased menstruating between 6 and 12 months prior to enrolment, biochemical evidence of menopause was required (FSH levels < 30 UI/1 or LH < 30 UI/I and oestradiol > 20 pg/I). For women who had undergone a hysterectomy without oophorectomy before menopause, the date of menopause was determined according to clinical (flushes) and biological criteria." Exclusion criteria: "Women with a documented history of alcoholism or with evidence from physical examination, laboratory tests or radiography of any bone metabolism disorder were also excluded. We also excluded women undergoing treatment which might interfere with bone metabolism." Age: 53.8 (3.1) years Time since menopause: 2.6 (1.4) years BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: NR Previous bisphosphonate experience: NR Source: France, seven centres Race/ethnicity: Caucasian (100%)
Interventions	Two-arm comparison: • Etidronate: a cycle consisting of etidronate 400 mg/day for 14 days and followed by calcium 500 mg/day for 77 days was repeated for two years • Control: calcium 500 mg/day, continuously
Outcomes	Clinical, non-vertebral, hip and atypical femoral fractures: all seemed to be reported as adverse events, in addition with two safety outcomes, withdrawals due to adverse events and serious adverse events. All adverse events, regardless of their severity or relationship to etidronate, were assessed at each visit. A serious adverse event was defined as death, overdose, a diagnosis of cancer, or any event that was life-threatening, permanently disabling, required patient hospitalization, or extended hospitalization. All outcome data were extracted from the 2-year treatment period.
Notes	Funding information: NR. One of ten authors was employed by "Procter & Gamble Pharmaceuticals, Neuilly sur Seine".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“This was a multi-centre (seven centres), double-masked, placebo-controlled, randomized study.” The method for sequence generation was not provided.

Pouilles 1997 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"…double-masked …" Blinding approach was not provided. It was not clear if the blinding was effective to prevent the participants and personnel from knowing the assigned treatment.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Blinding approach was not provided. Judged to be at low risk of bias given that the incidence of objective outcomes were based on clinical judgements (criteria), in addition to participants' signs and symptoms, which were less likely to be influenced, even if the blinding was ineffective.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	As above, but judged to be at unclear risk of bias given that assessment of subjective outcomes would possibly be influenced by the participants' and assessors' knowledge of the allocated interventions if the blinding was not effective.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"All analyses were performed for the intent-to-treat (ITT) population comprising all women who were randomized to treatment and who had been given etidronate or placebo." Fracture incidence was recorded as safety outcome. In this 2-year study, 84% (46/55) and 83% (45/55) of the randomized participants in the placebo and etidronate groups completed the study and were included in the analyses, respectively. Judged to be at low risk of bias given that the completion rates were greater than 80%, the numbers and reasons for discontinuation appeared balanced between the groups, and the unreported missing data seemed unlikely to significantly bias the outcome estimate.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	As above: judged to be at low risk of bias given that the completion rates were good and the portion of missing data was unlikely to significantly bias the safety outcome estimate.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as described in the method section.
Other bias	Low risk	It was a 3-year study, with the final year without any active drug in both groups. The outcomes data were all extracted from the 2-year on-treatment results. It appeared to be free of other risks of bias.

Russo 1996

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: 12 months Blinding: NR Trial completion: NR/77 • Etidronate: NR/31 • Alendronate: NR/38 • Intermittent/cyclic clodronate: NR/8

Russo 1996 *(Continued)*

Participants	Inclusion criteria: BMD lower than the mean value in normal population -2.5 SD (Z-score) in at least two of the sites measured at the radius; duration of physiological menopause at least one year; and age 50 to 77 years. Exclusion criteria: previous vertebral and long bone fractures; pathologies interfering with bone metabolism, such as nephropathies, endocrinopathies, malabsorption, etc.; previous anti-osteoporotic treatment, or treatment with drugs (corticosteroids, heparin, calcium salts, vitamin D, etc.) acting on bone metabolism during the previous month Age: 64.1 (6.2) years Time since menopause: 14.7 (6.6) years BMI: 26.9 (0.8) kg/m^2 Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 0% Previous bisphosphonate experience: 0% Source: Italy Race/ethnicity: NR
Interventions	Three-arm comparison: • Etidronate 400 mg/day for the first 14 days, followed by calcium carbonate 1250 mg/day from day 15 to 90, for 4 cycles • Alendronate 5 mg/day for 12 months • Intermittent/cyclic clodronate: sodium clodronate 100 mg/day, IM during the first 20 days, followed by a 10-day interval, then 400 mg/day for two months, then followed by a 1-month interval, and then repeat the whole cycle.
Outcomes	Radiographic vertebral fractures: "Pre- and post-treatment X-rays of the dorso-lumbar area of the spine were obtained, and radiological analysis used Meunier-Vignon's index for vertebral deformation." Non-vertebral, hip, wrist and clinical vertebral fractures: previous fractures were recorded in the patients' case history, but the authors gave no details/insufficient information about assessment methods. It was not clear if the fractures were reported as efficacy outcomes. Investigators assessed two safety outcomes, including withdrawals due to adverse events and serious adverse events, but did not provide sufficient information about assessment methods.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"…77 postmenopausal women randomly divided into 3 groups…" Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.

Russo 1996 *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and blinding approach was not provided. In this study, blinding does not seem feasible because it involved different regimens and different administering methods. The participants and the personnel were likely not blinded and their performance was likely influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judged to be low risk of bias given that the assessment of objective outcomes were based on objective evidence or clinical criteria, which would be less likely to be impacted by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	As above, but judged to be at high risk of bias given that the subjective outcomes would probably be influenced by the participants' or assessors' knowledge of the allocated interventions if blinding was not performed or was ineffective.
Incomplete outcome data (attrition bias) Efficacy outcomes	Unclear risk	Statistical analyses and attrition are not reported. It was not clear if all the randomized participants were included in the analysis. In addition, all fracture outcomes of interest are reported as safety outcomes and inferred from "...no other fractures occurred in any of the subjects." Numbers and reasons for withdrawals in two groups were not reported.
Incomplete outcome data (attrition bias) Safety outcomes	Unclear risk	As above: judged as unclear risk of bias given the insufficient information. Withdrawals and reasons were not reported.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the outcomes of interest were reported as described in the method section.
Other bias	Unclear risk	The lack of information in the methods section made it impossible to judge the risk of bias from other domains.

Sahota 2000

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: 60 weeks Blinding: open-label Trial completion: 132/140 (94%) • Etidronate: 36/36 (100%) • Alendronate, continuous: 31/37 (84%) • Alendronate, cyclic: 32/33 (97%) • Calcitriol: 33/34 (97%)
Participants	Inclusion criteria: aged ≥ 60 years (range 60 to 82 years) with vertebral osteoporosis were recruited from the metabolic clinic over a 12-month period. All patients were independent in activities of daily living, resident in their own homes, and had at least one or more vertebral osteoporotic fractures. Exclusion criteria: "The housebound, institutionalised and patients with vitamin D insufficiency (25 hydroxyvitamin D<30 nmol/l) were excluded from the study, as were patients with a history of peptic or esophageal disease requiring prescription medication within the previous 3 years and/or with disease known to affect bone metabolism. Exclusion criteria for medication included the ever use of bisphos-

Sahota 2000 *(Continued)*

	phonate, calcitonin or sodium fluoride and/or the use within the previous 5 years of hormone replacement therapy, glucocorticoids, androgens, anabolic steroids or vitamin D/calcium supplements." Age: 68.6 (4.9) years Time since menopause: 18.6 (4.1) years BMI: 26.0 (3.0) kg/m^2 Lumbar spine BMD: 0.81 (0.08) g/cm^2 Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: 0% Source: the UK, a metabolic clinic Race/ethnicity: NR
Interventions	Four-arm comparison: • Etidronate: cyclical etidronate (Didronel PMO) 400 mg/day for 14 days, followed by daily calcium carbonate 1.25 g (equivalent to 500 mg calcium) for 76 days. The 3-month cycle was repeated for 12 months. • Alendronate, continuous: alendronate 10 mg, once daily for 12 months • Alendronate, cyclic: alendronate 10 mg, once daily in 3-monthly cycles on/off • Calcitriol: 0.25 µg twice daily
Outcomes	None of the fracture outcomes were extracted. Investigators assessed withdrawals due to adverse events but did not provide sufficient information about assessment methods.
Notes	Funded by an educational grant from Procter & Gamble and Roche Pharmaceutical Limited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized by computer-generated randomization codes into four treatment arms."
Allocation concealment (selection bias)	Unclear risk	As above, but the method for allocation concealment was not provided
Blinding of participants and personnel (performance bias)	High risk	"...a 12 month open, randomized controlled, prospective trial." It was an open-label trial, where participants' and personnel's knowledge about the allocated interventions would likely influence their performance during the study.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	It was an open-label trial, in which the participants' and the assessors' knowledge about the allocated interventions would likely bias their assessment for subjective outcomes.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	Only the outcome of withdrawal due to adverse events was extracted. All randomized participants seemed to be included in the analysis. The 1-year completion rates were 84% (31/37), 97% (32/33), 100% (36/36), and 97% (33/34) in

Sahota 2000 *(Continued)*

		continuous alendronate, cyclic alendronate, etidronate and calcitriol group, respectively. The overall completion rate was 132/140 (94%). It was judged to be at low risk of bias given the high and similar completion rates across groups.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available but the outcomes of interest were reported as described in the methods section. However, there seemed to be no monitoring or reporting of safety outcomes, except for withdrawals due to adverse events, which does not meet the standard reporting practices of clinical trials.
Other bias	Low risk	It appeared to be free of other risks of bias.

Shiota 2001

Study characteristics	
Methods	Randomized controlled trial Secondary prevention Duration: 2 years Blinding: NR Trial completion: NR/40 • Etidronate: NR/20 • Control: NR /20
Participants	Inclusion criteria: "Women over age 50 with postmenopausal osteoporosis diagnosed by DEXA BMD of < 0.70 g/cm^2 (WHO criteria > 2.5 SD below young adult mean.)" Exclusion criteria: women with fractures between L2 and L4 Age: 61.7 (6.7) years Time since menopause: 14.6 (7.9) years BMI: NR Lumbar spine BMD: 0.57 (0.08) g/cm^2 Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 60% Previous bisphosphonate experience: NR Source: Japan, one orthopaedic surgery outpatient clinic Race/ethnicity: Asian (100%)
Interventions	Two-arm comparison: • Etidronate 400mg/day for 2 weeks, followed by calcium lactate 2 g/day and alphacalcidol 0.5 µg/day for 10 weeks (12-week cycle repeated 8 times) • Control: daily calcium lactate 2 g and alphacalcidol 0.5 µg

Shiota 2001 *(Continued)*

Outcomes	Radiographic vertebral fractures: "Compression fracture defined according to the criteria of the Japanese Society for Bone and Mineral Research, which is based on ratios of centre (C), anterior (A) and posterior (P) heights of each vertebra in the lateral view of thoraco-lumbar X-rays. If either C/A or C/P was below 0.8, or A/P was below 0.75, this was assessed as the presence of a compression fracture. In patients with vertebra plana, a fracture was diagnosed if centre, anterior and posterior heights were <80% of the values of adjacent vertebrae. The number of fractures was counted at baseline and final assessment." Serious adverse events: zero events were inferred from "no adverse effects of the treatment were noted" in the text. Assessment methods were not provided.
Notes	Funding information: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly assigned to two groups." Method for sequence generation not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and blinding approach was not provided. The participants and the personnel were likely not blinded and their performance might have been influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"A compression fracture was defined according to the criteria of the Japanese Society for Bone and Mineral Research…The number of fractured vertebrae was counted on the X-ray films before the treatment and at the final assessment." Although it was likely an open-label study, the reported fracture outcome was assessed with radiographic evidence, in addition to participants' sign and symptoms. Judged to be at low risk of bias.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	It was likely an open-label study. The reporting and assessment for the subjective outcomes were likely influenced by the participants' and/or assessors' knowledge of the allocated interventions after assignment.
Incomplete outcome data (attrition bias) Efficacy outcomes	Unclear risk	All the randomized participants included in the analysis (Fig. 2). Not clear if there was any discontinuation in this 2-year study.
Incomplete outcome data (attrition bias) Safety outcomes	Unclear risk	"No adverse effects of the treatment were noted by any of the patients in either group, and serum calcium, phosphorus, and alkaline phosphatase levels remained within the normal ranges." Not clear if all the randomized participants were included in the analysis and if there was any discontinuation in this 2-year study.
Selective reporting (reporting bias)	Low risk	Protocol was not available. However, the reported outcomes in the results section appeared to be pre-specified in the method section.
Other bias	Low risk	None were identified.

Steiniche 1991

Study characteristics	
Methods	Randomized, active-controlled trial Secondary prevention Duration: 60 weeks Blinding: NR Trial completion: 31/37 (84%) • Etidronate: 16/19 (84%) • ADFR: 15/18 (83%)
Participants	Inclusion criteria: postmenopausal women aged 55 to 75 years, with spinal osteoporosis. All participants had at least one and not more than four spontaneous fractures in the spine. Exclusion criteria: immobilisation, abnormal liver or kidney function, receiving drugs with known effects on calcium or bone metabolism. Age: 67 (NR) years Time since menopause: NR BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: NR Source: Denmark Race/ethnicity: NR
Interventions	Two-arm comparison: • Etidronate: 400 mg/day for 2 weeks, followed by 13 weeks off treatment. The 15-week treatment cycle was then repeated four times. • ADFR: triiodothyronine 100 µg/day for 7 days, followed by oral etidronate 400 mg/day for 2 weeks; the drug-free period until next activation was 12 weeks. The 15-week treatment cycle was then repeated four times. Both groups received daily elemental calcium 120 mg (as 500 mg calcium phosphate) and 400 IU vitamin D_3 during the study period.
Outcomes	None of the fracture outcomes were extracted. Serious adverse events and gastrointestinal adverse events: the clinical status and well-being of each participant were evaluated at each visit every three months during the study. Zero serious adverse events were inferred from the text: "minor or not clinically significant".
Notes	Funding information: the study was supported in part by a research grant from Norwich Eaton Pharmaceuticals, Inc., a Proctor & Gamble Company.
Risk of bias	

Steiniche 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Thirty-seven patients were randomized to receive ..." The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned; it was probably an open-label trial because of the different regimens. Judged to be at high risk of bias given the open-label design where the participants' and personnel's knowledge about the allocated interventions would likely influence their performance during the study.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	It was probably an open-label trial in which the reporting and the assessment for subjective outcomes might have been influenced by the participants' and/or the assessors' knowledge about the allocated interventions.
Incomplete outcome data (attrition bias) Safety outcomes	Unclear risk	"Sixteen patients in the intermittent cyclic etidronate group and 15 in the ADFR group completed 60 weeks of treatment. " Statistical methods for safety analysis were not provided. Information about the attrition was not given.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the reported outcomes appeared to be pre-specified in the methods section.
Other bias	Low risk	It appeared to be free of other risks of bias.

Storm 1990

Study characteristics	
Methods	Randomized, placebo-controlled trial Secondary prevention Duration: 3 years Blinding: double-blind Trial completion: 40/66 (61%) • Etidronate: 20/33 (61%) • Placebo: 20/33 (61%)
Participants	Inclusion criteria: postmenopausal women with osteoporosis defined as 1 to 4 atraumatic vertebral crush fractures and radiographically-confirmed demineralisation of vertebrae. Exclusion criteria: secondary causes of osteoporosis e.g. hyperthyroidism, Paget's disease, renal osteodystrophy; impairment of renal, cardiac or thyroid function. Treatment with corticosteroids, oestrogens, calcitonin, calcium or vitamin D; 3 months in the previous 6 months or any of the previous 2 months. History of fluoride or diphosphonate therapy. Age: 68.4 (0.9) years Time since menopause: 21.6 (1.3) years BMI: NR

Storm 1990 *(Continued)*

	Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: 0% Source: Denmark Race/ethnicity: NR
Interventions	Two-arm comparison: • Etidronate 400mg/day for 2 weeks, followed by 13 weeks of no drug (10 cycles) • Placebo for 2 weeks, followed by 13 weeks of no drug (10 cycles) Daily calcium 500 mg and Vitamin D 400 IU were given to all the participants throughout the study.
Outcomes	Non-vertebral, hip and wrist fractures: both spontaneous and traumatic, clinically-overt fractures were included and the time of occurrence during the study was recorded. Withdrawals due to adverse events: all side effects and deaths that occurred were recorded, and their causes were evaluated. Withdrawals due to adverse events were composed of intercurrent illness and death.
Notes	Funding by Norwich Eaton Pharmaceuticals, a Procter & Gamble company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"…randomized…" "The patients were assigned to one of two study groups by means of computer-generated random numbers."
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"…double-blind, placebo-controlled study." Blinding approach was not provided. It was not clear if the participants and the personnel were blinded appropriately and whether their performance was influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"…double-blind, placebo-controlled study... Radiographs of the thoracic (T-4 to T-12) and lumber (L-1 to L-4)…were evaluated by an independent radiologists who was unaware of the patients' assigned group." Blinding approach was not provided, but we judged study to be at low risk of bias given that the objective outcomes were based on radiographic evidence and objective clinical criteria, which were less likely to be influenced by ineffective blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	As above, but we judged study to be at unclear risk of bias given that the reporting and the assessment of subjective outcomes might have been influenced by the participants' and/or assessors' knowledge of the allocated interventions if blinding was not effective.
Incomplete outcome data (attrition bias)	High risk	It was not clear if all the randomized population was included in the analysis. In this 3-year trial, 61% of the participants in each of the groups completed the

Storm 1990 *(Continued)*

Efficacy outcomes		study, and the numbers and reasons for the early discontinuations appeared balanced across groups. Judged to be at high risk of bias given that the overall completion rate was less than 80% and the approach to handling missing data was not provided.
Incomplete outcome data (attrition bias) Safety outcomes	High risk	As above: judged to be at high risk of bias given the comparatively low completion rates and the lack of an appropriate approach to handling the missing data.
Selective reporting (reporting bias)	High risk	Protocol was not available but the pre-specified outcomes appeared to be reported consistently. However, serious adverse events were not reported, and 10 deaths (5 in each group) were reported for withdrawals. We suspect the study overlooked some important (safety) results.
Other bias	Low risk	None were observed.

Tobias 1997

Study characteristics	
Methods	Randomized, placebo-controlled trial Primary prevention Duration: two years Blinding: double-blind Trial completion: NR/46 • Etidronate: NR/24 • Placebo: NR/22
Participants	Inclusion criteria: "Post-menopausal women within 7 [years] of the menopause, who had a lumbar spine bone mineral density (BMD) (L2–4) within the lowest quartile of our local reference range (London, the UK), were recruited over 12 months." Exclusion criteria: post-menopausal women who had received treatment with hormone replacement therapy (HRT) within the previous 6 months, or had evidence of a vertebral fracture on thoraco-lumbar spine radiographs. Age: NR Time since menopause: NR BMI: NR Lumbar spine BMD: NR Femoral neck BMD: NR Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 0% Previous bisphosphonate experience: NR Source: the UK Race/ethnicity: NR

Tobias 1997 *(Continued)*

Interventions	Two-arm comparison: • Etidronate: 8 cycles of 14-day treatment with etidronate 400 mg/day followed by calcium 500 mg/day (Cacit) for 76 days • Placebo: 8 cycles of 14-day treatment with placebo, followed by calcium 500 mg/day (Cacit) for 76 days
Outcomes	None of the fracture outcomes were reported. Withdrawals due to adverse events: reasons for early discontinuations in each group were described, but the authors gave no details/insufficient information about assessment methods
Notes	Funding information: NR The study was published in a letter format.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized to receive..." The method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	The method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"...a double-blind placebo-controlled study." Blinding approach was not provided. It was not clear if the blinding was effective to prevent the participants and the personnel from knowing the assigned treatments.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	"...a double-blind placebo-controlled study." Blinding approach was not provided. It was not clear if the blinding was effective to prevent the participants and the assessors from knowing the assigned treatments and whether their reporting and assessment of the subjective outcomes were influenced.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	Only one safety outcome, withdrawals due to adverse events, was reported. The reasons for early discontinuations were described and all the randomized participants seemed to be included. Judged to be at low risk of bias.
Selective reporting (reporting bias)	Unclear risk	Protocol was not available and the report was very brief (a letter to the editor). It was not clear whether the pre-planned outcomes were reported properly.
Other bias	Unclear risk	The study was published in a brief letter format and information about attrition was not given. It was not clear whether there were other risks of bias, given the limited information.

Watts 1990

Study characteristics

Methods	Randomized, placebo-controlled trial Secondary prevention Duration: 2 years

Watts 1990 *(Continued)*

	Blinding: double-blind Trial completion: 363/429 (85%) • Etidronate: 92/105 (88%) • Placebo: 90/105 (86%) • Etidronate + phosphate: 93/107 (87%) • Placebo+phosphate: 88/106 (83%)
Participants	Inclusion criteria: generally healthy, white and Asian women age 75 or younger who had been post-menopausal for at least 12 months. Weight between 40 kg and 80 kg. All had osteoporosis, defined as 1 but not more than 4 vertebral compression fractures plus radiographic evidence of osteopenia. Exclusion criteria: treatment with oestrogen, steroids, glucocorticoids, phosphate or calcium > 1.0 g/day or vitamin D > 1000 IU/day in previous 6 months. Treatment with thiazide in previous 2 months or any treatment with fluoride, calcitonin or bisphosphonate. Secondary osteoporosis or any medical conditions that might confound participation (e.g. active rheumatoid arthritis, active gastrointestinal or liver disease, chronic alcoholism, or renal impairment as evidenced by a serum creatinine level of more than 210 µmol/per litre). Age: 65.1 (0.6) years Time since menopause: 17.9 (0.9) years BMI: NR Lumbar spine BMD: 0.87 (0.02) g/cm^2 Femoral neck BMD: 0.68 (0.01) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: 0% Source: the USA, seven centres Race/ethnicity: Caucasian and Asian (numbers NR)
Interventions	Four-arm comparison: • Etidronate: placebo for days 1 to 3, followed by etidronate 400 mg/day for days 4 to 17 and calcium 500 mg/day for days 18 to 912. • Placebo: placebo for days 1 to 17, followed by calcium 500 mg/day for days 18 to 913. • Etidronate + phosphate: phosphate 1 g twice daily for days 1 to 3, followed by etidronate 400 mg/day for days 4 to 17 and calcium 500 mg/day for days 18 to 914. • Placebo + phosphate: phosphate 1 g twice daily for days 1 to 3, followed by placebo for days 4 to 17 and calcium 500 mg/day for days 18 to 91. Cycles of each group were repeated every 91 days for 2 years, which followed the ADFR (activation, depression, treatment-free, repeat) regimen.
Outcomes	Radiographic vertebral fractures: lateral radiographs of thoracic and lumbar spine performed at baseline, 12 and 24 months, and were reviewed by a single-blinded radiologist. A new fracture was defined as a reduction of 20% or more in anterior, middle, or posterior height with a reduction of 10% or more in the area of a previously unfractured vertebra. Non-vertebral, hip and wrist fractures: the authors gave no details/insufficient information about assessment methods.

Watts 1990 *(Continued)*

	One safety outcome, withdrawals due to adverse events, was reported. Participants were asked to report adverse events by phone and questioned about symptoms and intercurrent illnesses at each visit.
Notes	Funded by Norwich Eaton Pharmaceuticals, a Procter & Gamble company. For meta-analysis, we treated Watts 1990 as two pair-wise comparisons of etidronate versus placebo. We compared arms 1 and 2. We redefined the third arm (which gave participants phosphate 2 g/day for days 1 to 3, etidronate 400 mg/day for days 4 to 17, then calcium 500 mg/day for days 18 to 914) as an experimental arm - 'etidronate 400 mg/day' - and compared it to the fourth arm, a placebo arm (participants were given phosphate 2 g/day for days 1 to 3, placebo for days 4 to 17, then calcium 500 mg/day for days 18 to 91).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"…randomized… The patients were randomly assigned by computer to treatment groups in blocks of four."
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"…double-blind, placebo-controlled study." The blinding method was not provided. It was not clear if the blinding was effective to prevent participants and personnel from knowing the allocated interventions and whether their performance would have been influenced.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"These radiographs were evaluated visually by a single radiologist who did not know the patient's treatment group. Each patient's series of films was displayed simultaneously on adjacent view boxes in chronologic order. A new vertebral fracture was defined as…" The approaches to maintaining the assessor's blindness were provided. Assessments of objective outcomes were less likely to be influenced.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	A double-blind study, but the approaches to maintaining the participants' or assessors' knowledge of the allocated interventions for other safety outcomes were not provided. Judged to be at unclear risk of bias.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"The results are expressed as the means ± SE and reflect results from all patients who began the study regimen." In this two-year trial, 86% (89/104), 83% (89/107), 88% (92/105), and 87% (90/104) of the participants in placebo, placebo + phosphate, etidronate + placebo, and etidronate + phosphate group completed the study, respectively. Specifically for vertebral fracture, 88.7 % (375/423) of the randomized who had "spinal radiography obtained at entry and after 12 or 24 months (or both)" (Table 3) are included. The 'last observation carried forward' approach seems to have been used to handle the missing data. It was not clear about the other fracture outcomes. Given the good completion rates, we judged it to be at low risk of bias (although there was no appropriate approach to handling the missing data).
Incomplete outcome data (attrition bias) Safety outcomes	Unclear risk	As above: the completion rates were good and appeared balanced across groups. However, two deaths judged to be irrelevant to the study were not included as withdrawals due to adverse events, and not reported by groups. The description of "...26 had intercurrent illnesses..." was insufficiently clear to make a judgement about risk of bias. It was not clear whether and how the missing data would have affected the estimate effect size.

Watts 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol was not available, but the reported outcomes appeared to be prespecified.
Other bias	Low risk	None were identified.

Wimalawansa 1995

Study characteristics	
Methods	Randomized, active-controlled trial Primary prevention Duration: 4 years Blinding: NR Trial completion: 45/58 (78%) • Etidronate: 10/14 (71%) • HRT: 12 /15 (80%) • Etidronate + HRT: 12/15 (80%) • Control: 9/14 (64%)
Participants	Inclusion criteria: "White women whose postmenopausal status was established with serum gonadotropin and 17B-estradiol levels. All patients were within 1 and 5 years of the onset of natural menopause and bone mineral density was within the reference range established with normal healthy women aged between 30 and 40 years. None of them had an oophorectomy or spinal, wrist, or hip fractures; and secondary causes of osteoporosis were excluded." Exclusion criteria: receiving any medication known to affect calcium metabolism. Previous treatment with HRT or bisphosphonates. Age: 52.6 (0.5) years Time since menopause: 3.2 (0.34) years BMI: 24.4 (0.80) kg/m^2 Lumbar spine BMD (SEM): 0.89 (0.01) g/cm^2 Femoral neck BMD: 0.72 (0.01) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 0% Previous bisphosphonate experience: 0% Source: the UK Race/ethnicity: Caucasian (100%)
Interventions	Four-arm comparison: • Etidronate, intermittently and cyclically administered 400 mg/days for 14 days, followed by 10 weeks of 1 g/day of calcium • HRT: 17B-E2 2.5 g/day [percutaneous Oestrogel, equivalent of daily 7B-E2.5 mg] + micronized progesterone 200 mg/day for 12 days each month + 1 g/day elemental calcium supplements

Wimalawansa 1995 *(Continued)*

	• Etidronate + HRT: combined use of cyclical etidronate and HRT, with elemental calcium supplements 1 g/day • Control: 1 g/day calcium supplementation only
Outcomes	None of the fracture outcomes were reported. Withdrawals due to adverse events: the authors gave no details/insufficient information about assessment methods.
Notes	Funding information: not funded by industry. We used data from the four reported groups, and analysed these as five pairwise comparisons: etidronate versus HRT, etidronate versus (etidronate + HRT), etidronate versus control, (etidronate + HRT) versus HRT, and (etidronate + HRT) versus control.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Fifty-eight early postmenopausal women attending metabolic bone disease outpatient clinics were randomly allocated..." Method for sequence generation was not provided.
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and blinding approach was not reported. It was likely an open-label trial given there were four different interventions (etidronate, HRT (oestrogen/progesterone), etidronate + HRT combination, and calcium only) administered with varying frequencies. The participants and the personnel were likely not blinded; their performance might have been influenced.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	As above: likely an open-label trial, in which the participants and the assessors were likely not blinded and their reporting and assessment of the subjective outcomes might have been influenced.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	Only one safety outcome, withdrawals due to adverse events, was reported. It appears that all the randomized participants were accounted for and there was no attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting was found.
Other bias	Low risk	No other risk of bias was detected.

Wimalawansa 1998

Study characteristics

Methods	Randomized controlled trial Secondary prevention Duration: 4 years Blinding: NR, but the radiologist who read the X-rays was blinded

Wimalawansa 1998 *(Continued)*

	Trial completion: 58/72 (81%) • Etidronate: 14/17 (82%) • HRT: 15/18 (83%) • Etidronate + HRT: 15/19 (79%) • Control: 14/18 (78%)
Participants	Inclusion criteria: "Postmenopausal Caucasian women with osteoporosis defined as 1 but not more than 4 radiographically demonstrable atraumatic thoracic vertebral crush fractures and spine DXA BMD 2.0 SD below age 35 normal reference range." Exclusion criteria: surgical menopause, secondary osteoporosis, medical conditions affecting skeleton, medications affecting calcium metabolism in previous 3 years, any treatment with HRT, steroids, glucocorticoids, calcitonin, fluoride or bisphosphonates since menopause. Ag: 64.9 (0.9) years Time since menopause: 15.1 (0.8) years BMI: 24.8 (0.8) kg/ m^2 Lumbar spine BMD: 0.825 (0.01) g/cm^2 Femoral neck BMD: 0.663 (0.046) g/cm^2 Lumbar spine T-score: NR Femoral neck T-score: NR Prevalent vertebral fractures: 100% Previous bisphosphonate experience: 0% Source: NR (England or USA) Race/ethnicity: Caucasian (100%)
Interventions	Four-arm comparison: • Etidronate: etidronate 400mg/day for 14 days every 12 weeks • HRT: Premarin 0.625 mg/day and norgestrel 150 µg/day for 12 days per month • Etidronate + HRT: each of the drugs was at the same doses as in arms 1 and 2 • Control: no treatment All women received daily calcium 1 g and vitamin D 400 IU throughout the study.
Outcomes	Radiographic vertebral fractures: "Lateral radiographs of thoracic (T4 to T12) and lumber (L1 to L4) spine performed at baseline and 4 years were read by a single radiologist blinded to sequence and therapy. A new fracture was defined as a reduction of 20% or more in anterior, middle, or posterior height with a reduction of 15% or more in the area of a previously unfractured vertebra. Further deterioration of the height or the area of a previously affected vertebra was not considered as a new fracture." Non-vertebral: clinically apparent non-vertebral fractures were assessed, but the authors gave no details/insufficient information about assessment methods Withdrawals due to adverse events: women were monitored at 3-month intervals for possible side effects.
Notes	Funding information: NR. We used data from the four reported groups, and analysed these as five pairwise comparisons: etidronate versus HRT, etidronate versus (etidronate + HRT), etidronate versus control, (etidronate + HRT) versus HRT, and (etidronate + HRT) versus control.

Wimalawansa 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A four-year randomized controlled trial…Using computer-generated random numbers, patients were allocated randomly into one of four treatment groups."
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not mentioned and no blinding method was provided. It was likely an open-label study because the four treatments had different use (number) of drugs and dose schedules. The participants and personnel were unlikely to be blinded and their performance might have been influenced by their knowledge about the assigned treatments.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	"All X-ray films (basal and at 4 years) were coded and read by one radiologist who was blinded to both sequence and therapy. A new vertebral fracture was defined as a reduction of 20% or more of the anterior, middle or posterior height, with a reduction of 15% or more in area in a previously unaffected vertebra." As above: likely an open-label active-control study. However, the assessor for fracture outcomes was blinded. The assessment of objective outcomes was based on clinical criteria and radiographic evidence, which were unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	As above: likely to be an open-label active-control study. Judged to be at high risk of bias because the reporting and assessment of subjective outcomes would probably be influenced by the participants' or assessors' knowledge of the allocated interventions if blinding was not conducted.
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	Statistical analysis was not provided, but only 4, 3, 3, 4 in control, HRT, cyclic etidronate, and combined group were excluded, respectively, from the analysis because of early discontinuations (Table 2), respectively. The overall completion rate was 90% in year 2 and 81% in year 4. Judged to be at low risk of bias given that the overall completion rates were all greater than 80%. The portion of missing data was unlikely to significantly bias the effect estimates.
Incomplete outcome data (attrition bias) Safety outcomes	Low risk	Only one safety outcome, withdrawals due to adverse events, was reported. Judged to be at low risk of attrition bias given that all (randomized) participants were accounted for, except for one lost to follow-up.
Selective reporting (reporting bias)	Low risk	Protocol was not available; however, the reported outcomes were as pre-specified in the methods section.
Other bias	Low risk	It appeared to be free of other risks of bias.

Participant characteristics: unless otherwise specified, participants' characteristics are presented as mean and standard deviation (SD). Information was extracted as reported in the original study, with minimal revisions; we summarized data when necessary. For the parameter of 'race/ethnicity', we understood 'Caucasian', as reported in some studies, to mean white.
Route of drug administration: unless otherwise specified, drugs were administered orally.
ADFR regimen: repeated cycles of activation, depression, free, repeat; **BMD:** bone mineral density; **BMI:** body mass index; **DEXA/DXA:** dual energy X-ray absorptiometry; **FSH:** follicle-stimulating hormone; **HRT:** hormone replacement therapy; **IM:** intramuscular injection; **IN:** intranasal spray; **IU:** international unit; **IV:** intravenous injection; **NR:** not reported; **NSAID:** non-steroidal anti-inflammatory drug; **QoL:** quality of life; **SC:** subcutaneous injection; **WHO:** World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Caffarelli 2010	Ineligible intervention/comparator
Fujita 1993	Ineligible population: does not exclusively include postmenopausal women
Fujita 2009	Ineligible population: does not exclusively include postmenopausal women
Heaney 1976	Duration of therapy < 1 year
Iwamoto 2002	Ineligible intervention/comparator
Iwamoto 2003a	Duration of therapy < 1 year
Kushida 2004	Ineligible population: does not exclusively include postmenopausal women
Miller 1999	Ineligible population: does not exclusively include postmenopausal women
Pearson 1997	Ineligible population: does not exclusively include postmenopausal women
Struijs 1996	Ineligible intervention/comparator
Yamaguchi 2005	Ineligible population: does not exclusively include postmenopausal women
Zhu 2004	Ineligible intervention/comparator

Characteristics of studies awaiting classification *[ordered by study ID]*

Clemente 1996

Methods	Randomized controlled trial Primary or secondary prevention; insufficient information to determine Duration: 2 years Blinding: NR Trial completion: NR/120 Etidronate + HRT: NR Etidronate: NR HRT + calcium: NR Control: NR
Participants	Inclusion criteria: NR, but the text read "120 women suffering from postmenopausal osteoporosis..." Exclusion criteria: NR
Interventions	Four-arm comparison:

Clemente 1996 *(Continued)*

	1. Etidronate + HRT: etidronate 400 mg/day for 14 days followed by calcium 1 g/day for 76 days, repeating the cycle every 90 days; HRT = 17β oestradiol 50 µg patches twice-weekly plus medroxyprogesterone acetate 2.5 mg/day 2. Etidronate: cyclic intermittent etidronate as in group 1 3. HRT + calcium: HRT and calcium as in group 1 4. Control: no treatment
Outcomes	None of the review's outcomes of interest were reported.
Notes	Funding information: NR This was a conference abstract.

Dogan 2001

Methods	Randomized controlled trial Primary or secondary prevention: insufficient information to determine Duration: 48 weeks Blinding: NR Trial completion: NR/90 Etidronate: NR Intranasal salmon calcitonin: NR Calcitriol: NR
Participants	Inclusion criteria: NR, but the text reads: "The aim of this study is to compare these alternative therapeutic regimens in the treatment of postmenopausal osteoporosis. Ninety patients were studied." Exclusion criteria: NR
Interventions	Three-arm comparison: 1. Etidronate, 400 mg/day for 2 weeks followed by calcium 500 mg/day alone for 10 weeks; this cycle was repeated four times. 2. Salmon calcitonin, IN 100 IU/day plus calcium 500 mg/day 3. Calcitriol 0.5 mg/day All participants, except for those in the etidronate group, received daily calcium 500 mg.
Outcomes	None of the review's outcomes of interest were reported.
Notes	Funding information: NR This was a conference abstract.

JapicCTI-050093

Methods	Randomized controlled trial Primary or secondary prevention: insufficient information to determine

JapicCTI-050093 *(Continued)*

	Duration: NR Blinding: NR Trial completion: NR/NR Etidronate: NR Alfacalcidol: NR
Participants	Inclusion criteria: primary osteoporosis; had none or one to four vertebral (T4-L5) fracture(s); menopausal or postmenopausal woman or man aged 50 to less than 77; can walk (hospitalization/outpatient), etc. Exclusion criteria: secondary osteoporosis; other diseases with reduced bone mass except secondary osteoporosis; radiographic finding that might affect the vertebral intensity, etc.
Interventions	Two-arm comparison: 1. Etidronate: NR 2. Alfacalcidol: NR
Outcomes	NR, but "Incidences of vertebral fracture, etc."
Notes	Funding information: Sumitomo Dainippon Pharma Co., Ltd. This was a registered protocol. Study information was limited and the results not reported.

Lozano-Tonkin 1996

Methods	Randomized controlled trial Primary prevention Duration: three years Blinding: NR Trial completion: NR/72 Etidronate: NR/37 Calcitonin, IN: NR/35
Participants	Inclusion criteria: NR, but the text read "A group of 72 postmenopausal women with established (18 with vertebral fractures) or densitometric osteoporosis (z-score <-2.00)..." Exclusion criteria: NR
Interventions	Two-arm comparison: 1. Etidronate 400 mg/day for 14 days followed by 76 days of 500 mg calcium supplements 2. Placebo etidronate daily for 14 days followed by 76 days 500 mg calcium supplements Background medication: NR
Outcomes	None of the review's outcomes of interest were reported.
Notes	Funding information: NR

Lozano-Tonkin 1996 *(Continued)*	
	This was a conference abstract.

Nozaki 2002	
Methods	Placebo-controlled, randomized controlled trial Secondary prevention Duration: one year Blinding: NR Trial completion: NR/30 Etidronate + HRT: NR/15 Placebo + HRT: NR/15
Participants	Inclusion criteria: oestrogen non-responders whose BMD continued to decrease by more than 1% per year for more than 1 year during treatment. The BMD of all the participants was less than 70% of the young adult mean (YAM). They were considered to meet the criteria for osteoporosis in Japan. Exclusion criteria: NR, but "none had a history of metabolic disease influencing bone remodelling or a family history of osteoporosis. None of them had had an oophorectomy or hysterectomy. They were non-smokers with no history of alcohol abuse. There were no remarkable abnormalities in their dietary history and daily exercise patterns according to a questionnaire completed at the time of enrolment in this study."
Interventions	Two-arm comparison: 1. Etidronate + HRT: etidronate 200 mg/day + HRT for 2 weeks followed by HRT + calcium 900 mg/day for 10 weeks 2. Placebo + HRT: placebo + HRT for 2 weeks followed by HRT + calcium 900 mg/day for 10 weeks HRT: daily conjugated equine oestrogen (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg. Each 12-week treatment was repeated four times for a total duration of 1 year.
Outcomes	None of the review's outcomes of interest were reported.
Notes	Funding information: NR

Route of drug administration: unless otherwise specified, drugs were administered orally.
BMD: bone mineral density; **BPs:** bisphosphonates; **HRT:** hormone replacement therapy; **IM:** intramuscular injection; **IN:** intranasal spray; **IU:** international unit; **IV:** intravenous injection; **NR:** not reported; **NSAIDs:** non-steroidal anti-inflammatory drugs; **SC:** subcutaneous injection; **SD:** standard deviation

DATA AND ANALYSES

Comparison 1. Etidronate 400 mg/day versus placebo - base case analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Clinical vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Clinical vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.44]
1.2 Non-vertebral fractures	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Non-vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.61]
1.2.2 Non-vertebral fractures, secondary	4	598	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.71, 1.58]
1.3 Hip fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 Hip fractures, primary	2	189	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.2 Hip fractures, secondary	2	283	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.17, 5.19]
1.4 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 Wrist fractures, secondary	2	140	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.13, 6.04]
1.5 Radiographic vertebral fractures	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 Radiographic vertebral fractures, primary	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
1.5.2 Radiographic vertebral fractures, secondary	3	487	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.26, 0.82]
1.6 Withdrawals due to adverse events	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 Withdrawals due to adverse events, primary	8	597	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.81, 2.47]
1.6.2 Withdrawals due to adverse events, secondary	4	624	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.54, 2.18]
1.7 Serious adverse events	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Serious adverse events, primary	5	497	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.52, 1.54]
1.7.2 Serious adverse events, secondary	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.8 Gastrointestinal adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 Gastrointestinal adverse events, primary	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.26, 1.14]
1.9 Atypical femoral fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 Atypical femoral fractures, primary	2	189	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

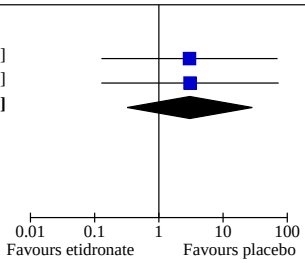
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.2 Atypical femoral fractures, secondary	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 1: Clinical vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Clinical vertebral fractures, primary						
Meunier 1997	1	27	0	27	50.2%	3.00 [0.13 , 70.53]
Pouilles 1997	1	54	0	55	49.8%	3.05 [0.13 , 73.37]
Subtotal (95% CI)		**81**		**82**	**100.0%**	**3.03 [0.32 , 28.44]**
Total events:	2		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

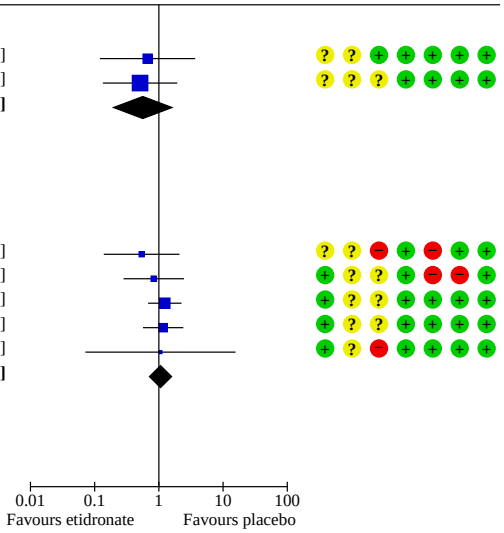
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 2: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Non-vertebral fractures, primary						
Meunier 1997	2	27	3	27	33.5%	0.67 [0.12 , 3.68]
Pouilles 1997	3	54	6	55	66.5%	0.51 [0.13 , 1.93]
Subtotal (95% CI)		**81**		**82**	**100.0%**	**0.56 [0.20 , 1.61]**
Total events:	5		9			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.2.2 Non-vertebral fractures, secondary						
Lyritis 1997	3	39	5	35	13.1%	0.54 [0.14 , 2.09]
Storm 1990	5	33	6	33	14.9%	0.83 [0.28 , 2.46]
Watts 1990	20	105	16	104	39.9%	1.24 [0.68 , 2.25]
Watts 1990 (1)	14	107	12	107	29.8%	1.17 [0.57 , 2.40]
Wimalawansa 1998	1	17	1	18	2.4%	1.06 [0.07 , 15.62]
Subtotal (95% CI)		**301**		**297**	**100.0%**	**1.06 [0.71 , 1.58]**
Total events:	43		40			
Heterogeneity: Chi² = 1.47, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.7%						



Footnotes

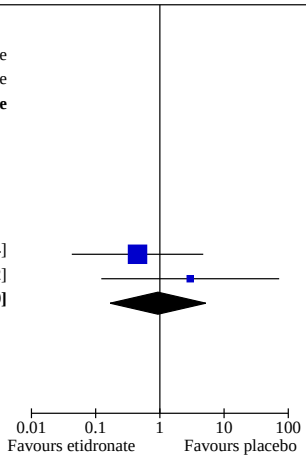
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 3: Hip fractures

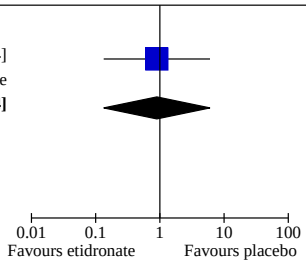
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.3.1 Hip fractures, primary								
Montessori 1997	0	40	0	40		Not estimable		+ ? − + − + ?
Pouilles 1997	0	54	0	55		Not estimable		? ? ? + + + +
Subtotal (95% CI)		**94**		**95**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.3.2 Hip fractures, secondary								
Lyritis 1997	1	39	2	35	80.8%	0.45 [0.04 , 4.74]		? ? − + − + +
Watts 1990	1	105	0	104	19.2%	2.97 [0.12 , 72.12]		+ ? ? + + + +
Subtotal (95% CI)		**144**		**139**	**100.0%**	**0.93 [0.17 , 5.19]**		
Total events:	2		2					
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 0.08 (P = 0.94)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 4: Wrist fractures

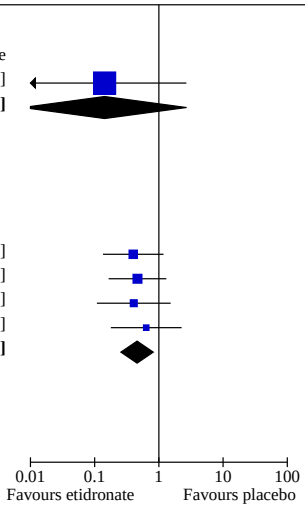
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.4.1 Wrist fractures, secondary								
Lyritis 1997	2	39	2	35	100.0%	0.90 [0.13 , 6.04]		? ? − + − + +
Storm 1990	0	33	0	33		Not estimable		+ ? ? + − − +
Subtotal (95% CI)		**72**		**68**	**100.0%**	**0.90 [0.13 , 6.04]**		
Total events:	2		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 5: Radiographic vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.5.1 Radiographic vertebral fractures, primary							
Herd 1997	0	75	0	77		Not estimable	? ? ? + + + +
Montessori 1997	0	40	3	40	100.0%	0.14 [0.01 , 2.68]	+ ? − + − + ?
Subtotal (95% CI)		**115**		**117**	**100.0%**	**0.14 [0.01 , 2.68]**	
Total events:	0		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							
1.5.2 Radiographic vertebral fractures, secondary							
Lyritis 1997	4	39	9	35	29.7%	0.40 [0.13 , 1.18]	? ? − + − + +
Watts 1990	5	98	10	91	32.5%	0.46 [0.16 , 1.31]	+ ? ? + + + +
Watts 1990 (1)	3	97	7	92	22.5%	0.41 [0.11 , 1.52]	+ ? ? + + + +
Wimalawansa 1998	3	17	5	18	15.2%	0.64 [0.18 , 2.26]	+ ? − + + + +
Subtotal (95% CI)		**251**		**236**	**100.0%**	**0.46 [0.26 , 0.82]**	
Total events:	15		31				
Heterogeneity: Chi² = 0.35, df = 3 (P = 0.95); I² = 0%							
Test for overall effect: Z = 2.64 (P = 0.008)							
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.44), I² = 0%							



Footnotes

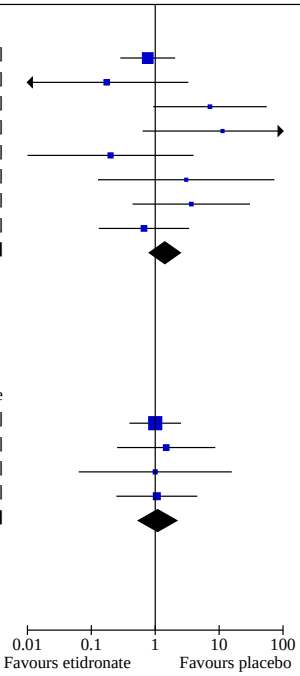
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 6: Withdrawals due to adverse events

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Withdrawals due to adverse events, primary						
Adami 2000	6	53	8	54	41.4%	0.76 [0.28 , 2.05]
Chilibeck 2002	0	14	2	12	14.0%	0.17 [0.01 , 3.29]
Heath 2000	7	38	1	39	5.2%	7.18 [0.93 , 55.65]
Herd 1997	5	74	0	76	2.6%	11.29 [0.64 , 200.69]
Meunier 1997	0	27	2	27	13.1%	0.20 [0.01 , 3.98]
Pouilles 1997	1	54	0	55	2.6%	3.05 [0.13 , 73.37]
Tobias 1997	4	24	1	22	5.5%	3.67 [0.44 , 30.35]
Wimalawansa 1995	2	14	3	14	15.7%	0.67 [0.13 , 3.40]
Subtotal (95% CI)		**298**		**299**	**100.0%**	**1.41 [0.81 , 2.47]**
Total events:	25		17			
Heterogeneity: Chi² = 11.33, df = 7 (P = 0.12); I² = 38%						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.6.2 Withdrawals due to adverse events, secondary						
Lyritis 1997	0	50	0	50		Not estimable
Storm 1990	7	33	7	33	54.2%	1.00 [0.39 , 2.53]
Watts 1990	3	105	2	104	15.5%	1.49 [0.25 , 8.71]
Watts 1990 (1)	1	107	1	107	7.7%	1.00 [0.06 , 15.78]
Wimalawansa 1998	3	17	3	18	22.5%	1.06 [0.25 , 4.54]
Subtotal (95% CI)		**312**		**312**	**100.0%**	**1.09 [0.54 , 2.18]**
Total events:	14		13			
Heterogeneity: Chi² = 0.16, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						



Footnotes

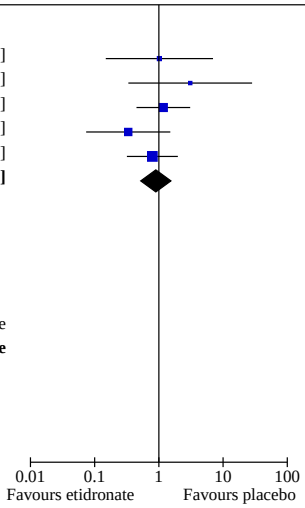
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 7: Serious adverse events

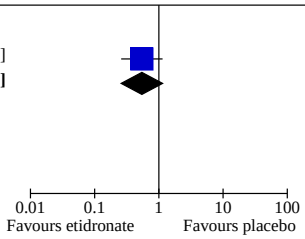
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.7.1 Serious adverse events, primary								
Adami 2000	2	53	2	54	8.0%	1.02 [0.15 , 6.97]		? ? ? ? − + +
Heath 2000	3	38	1	39	4.0%	3.08 [0.33 , 28.31]		? ? − − − + +
Herd 1997	8	74	7	76	27.9%	1.17 [0.45 , 3.07]		? ? ? ? + + +
Meunier 1997	2	27	6	27	24.2%	0.33 [0.07 , 1.51]		? ? + + + + +
Pouilles 1997	7	54	9	55	36.0%	0.79 [0.32 , 1.98]		? ? ? ? + + +
Subtotal (95% CI)		**246**		**251**	**100.0%**	**0.90 [0.52 , 1.54]**		
Total events:	22		25					
Heterogeneity: Chi² = 3.23, df = 4 (P = 0.52); I² = 0%								
Test for overall effect: Z = 0.40 (P = 0.69)								
1.7.2 Serious adverse events, secondary								
Lyritis 1997	0	50	0	50		Not estimable		? ? − − − + +
Subtotal (95% CI)		**50**		**50**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

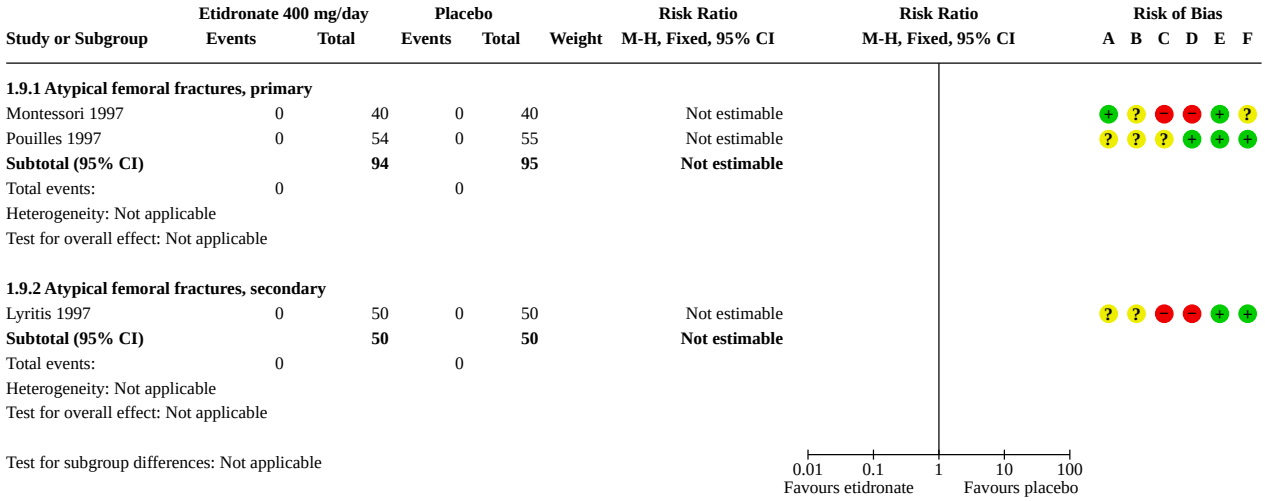
Analysis 1.8. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 8: Gastrointestinal adverse events

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.8.1 Gastrointestinal adverse events, primary								
Herd 1997	9	74	17	76	100.0%	0.54 [0.26 , 1.14]		? ? ? ? + + +
Subtotal (95% CI)		**74**		**76**	**100.0%**	**0.54 [0.26 , 1.14]**		
Total events:	9		17					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.61 (P = 0.11)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: Etidronate 400 mg/day versus placebo - base case analysis, Outcome 9: Atypical femoral fractures

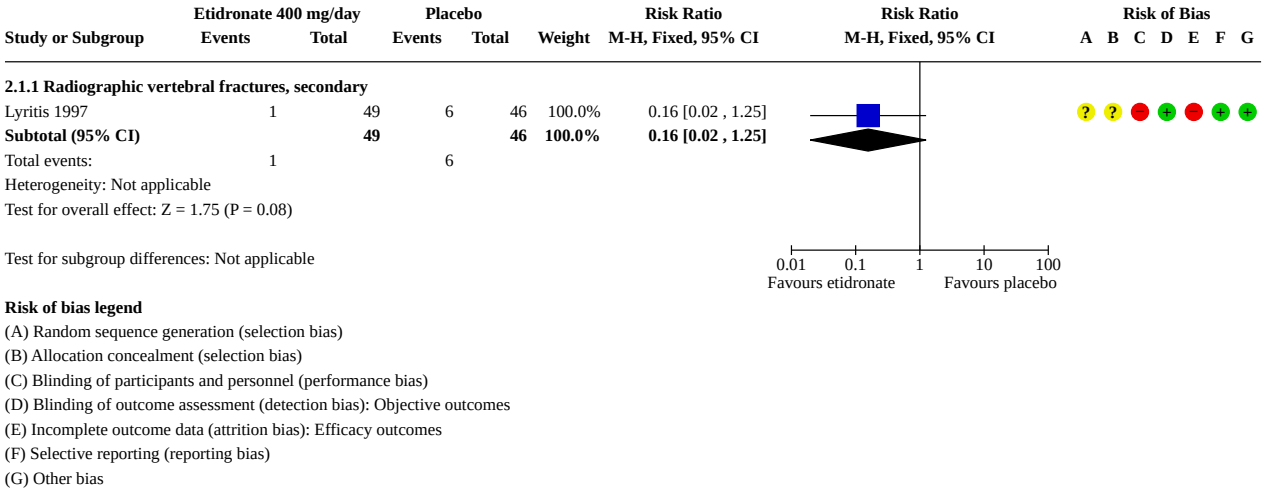


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Incomplete outcome data (attrition bias): Safety outcomes
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 2. Etidronate 400 mg/day versus placebo - subgroup of 1-year studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Radiographic vertebral fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 Radiographic vertebral fractures, secondary	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.25]

Analysis 2.1. Comparison 2: Etidronate 400 mg/day versus placebo - subgroup of 1-year studies, Outcome 1: Radiographic vertebral fractures



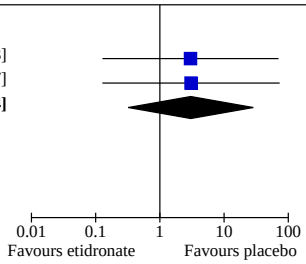
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Etidronate 400 mg/day versus placebo - subgroup of 2-year studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Clinical vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 Clinical vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.44]
3.2 Non-vertebral fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 Non-vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.61]
3.2.2 Non-vertebral fractures, secondary	1	423	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.76, 1.92]
3.3 Hip fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 Hip fractures, primary	1	109	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3.2 Hip fractures, secondary	1	209	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.12, 72.12]
3.4 Radiographic vertebral fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.4.1 Radiographic vertebral fractures, primary	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
3.4.2 Radiographic vertebral fractures, secondary	2	469	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.17, 0.67]

Analysis 3.1. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 1: Clinical vertebral fractures

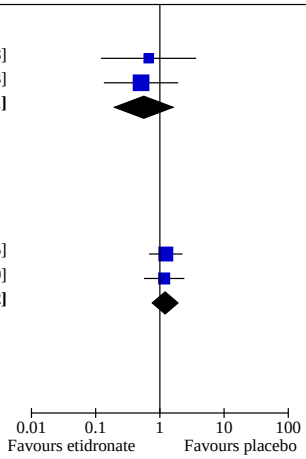
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.1.1 Clinical vertebral fractures, primary								
Meunier 1997	1	27	0	27	50.2%	3.00 [0.13 , 70.53]		? ? + + + + +
Pouilles 1997	1	54	0	55	49.8%	3.05 [0.13 , 73.37]		? ? ? + + + +
Subtotal (95% CI)		**81**		**82**	**100.0%**	**3.03 [0.32 , 28.44]**		
Total events:	2		0					
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 2: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.2.1 Non-vertebral fractures, primary								
Meunier 1997	2	27	3	27	33.5%	0.67 [0.12 , 3.68]		? ? + + + + +
Pouilles 1997	3	54	6	55	66.5%	0.51 [0.13 , 1.93]		? ? ? + + + +
Subtotal (95% CI)		**81**		**82**	**100.0%**	**0.56 [0.20 , 1.61]**		
Total events:	5		9					
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%								
Test for overall effect: Z = 1.08 (P = 0.28)								
3.2.2 Non-vertebral fractures, secondary								
Watts 1990	20	105	16	104	57.3%	1.24 [0.68 , 2.25]		+ ? ? + + + +
Watts 1990 (1)	14	107	12	107	42.7%	1.17 [0.57 , 2.40]		+ ? ? + + + +
Subtotal (95% CI)		**212**		**211**	**100.0%**	**1.21 [0.76 , 1.92]**		
Total events:	34		28					
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.80 (P = 0.42)								
Test for subgroup differences: Chi² = 1.71, df = 1 (P = 0.19), I² = 41.5%								

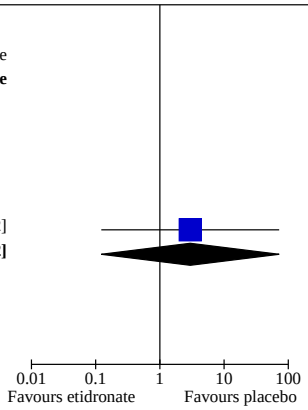


Footnotes
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.3. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 3: Hip fractures

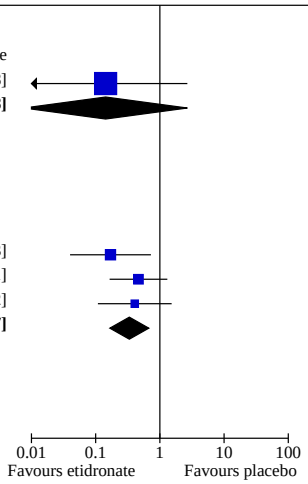
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.3.1 Hip fractures, primary							
Pouilles 1997	0	54	0	55		Not estimable	? ? ? + + + +
Subtotal (95% CI)		**54**		**55**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.3.2 Hip fractures, secondary							
Watts 1990	1	105	0	104	100.0%	2.97 [0.12 , 72.12]	+ ? ? + + + +
Subtotal (95% CI)		**105**		**104**	**100.0%**	**2.97 [0.12 , 72.12]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Etidronate 400 mg/day versus placebo - subgroup of 2-year studies, Outcome 4: Radiographic vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.4.1 Radiographic vertebral fractures, primary							
Herd 1997	0	75	0	77		Not estimable	? ? ? + + + +
Montessori 1997	0	40	3	40	100.0%	0.14 [0.01 , 2.68]	+ ? − + − + ?
Subtotal (95% CI)		**115**		**117**	**100.0%**	**0.14 [0.01 , 2.68]**	
Total events:	0		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							
3.4.2 Radiographic vertebral fractures, secondary							
Lyritis 1997	2	47	11	44	39.3%	0.17 [0.04 , 0.73]	? ? − + − + +
Watts 1990	5	98	10	91	35.9%	0.46 [0.16 , 1.31]	+ ? ? + + + +
Watts 1990 (1)	3	97	7	92	24.8%	0.41 [0.11 , 1.52]	+ ? ? + + + +
Subtotal (95% CI)		**242**		**227**	**100.0%**	**0.33 [0.17 , 0.67]**	
Total events:	10		28				
Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² = 0%							
Test for overall effect: Z = 3.08 (P = 0.002)							
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%							



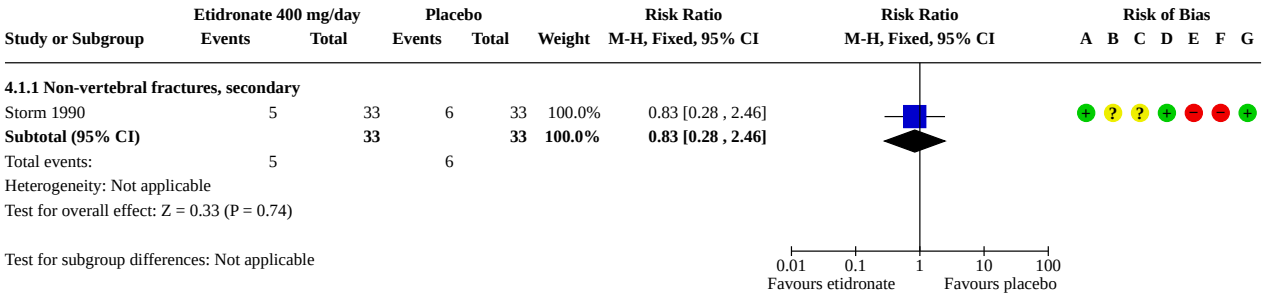
Footnotes
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4. Etidronate 400 mg/day versus placebo - subgroup of 3-year studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Non-vertebral fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 Non-vertebral fractures, secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.28, 2.46]
4.2 Hip fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 Hip Fractures, primary	1	80	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3 Wrist fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 Wrist fractures, secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.4 Radiographic vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 Radiographic vertebral fractures, primary	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
4.4.2 Radiographic vertebral fractures, secondary	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.82]

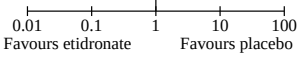
Analysis 4.1. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 1: Non-vertebral fractures



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 2: Hip fractures

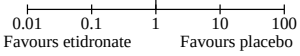
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
4.2.1 Hip Fractures, primary								
Montessori 1997	0	40	0	40		Not estimable		+ ? − + − + ?
Subtotal (95% CI)		**40**		**40**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

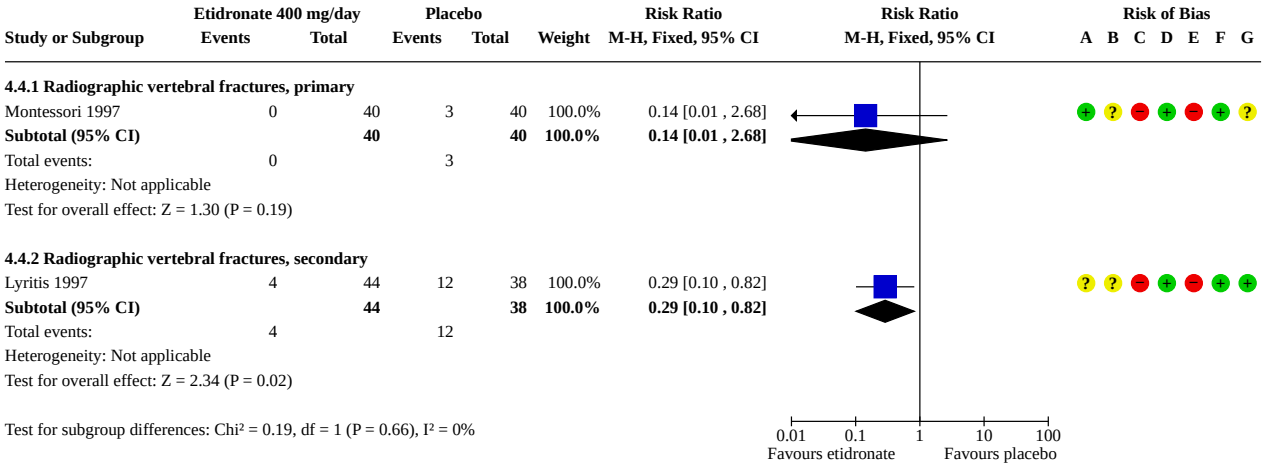
Analysis 4.3. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 3: Wrist fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
4.3.1 Wrist fractures, secondary								
Storm 1990	0	33	0	33		Not estimable		+ ? ? + − − +
Subtotal (95% CI)		**33**		**33**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: Etidronate 400 mg/day versus placebo - subgroup of 3-year studies, Outcome 4: Radiographic vertebral fractures



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 5. Etidronate 400 mg/day versus placebo - subgroup of 4-year studies

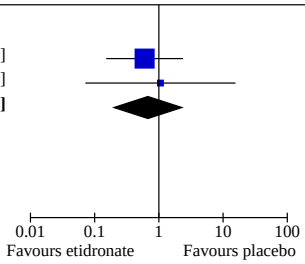
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Non-vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Non-vertebral fractures, secondary	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.20, 2.28]
5.2 Hip fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 Hip fractures, secondary	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.34]
5.3 Wrist fractures	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.3.1 Wrist fractures, secondary	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.39]
5.4 Radiographic vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.4.1 Radiographic vertebral fractures, secondary	2	109	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.21, 1.09]

Analysis 5.1. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 1: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Non-vertebral fractures, secondary						
Lyritis 1997	3	50	5	50	83.7%	0.60 [0.15 , 2.38]
Wimalawansa 1998	1	17	1	18	16.3%	1.06 [0.07 , 15.62]
Subtotal (95% CI)		**67**		**68**	**100.0%**	**0.67 [0.20 , 2.28]**
Total events:	4		6			

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable



Risk of Bias: A B C D E F G

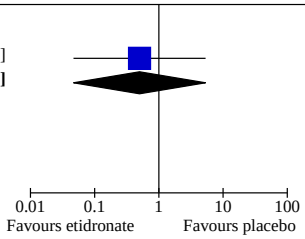
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 2: Hip fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Hip fractures, secondary						
Lyritis 1997	1	50	2	50	100.0%	0.50 [0.05 , 5.34]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.50 [0.05 , 5.34]**
Total events:	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

Test for subgroup differences: Not applicable

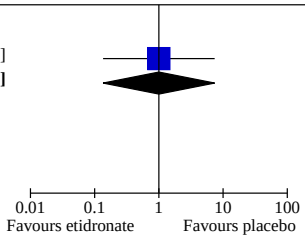


Risk of Bias: A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.3. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 3: Wrist fractures

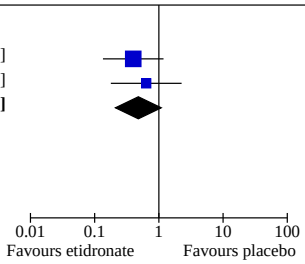
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
5.3.1 Wrist fractures, secondary								
Lyritis 1997	2	50	2	50	100.0%	1.00 [0.14 , 7.39]		? ? − + − + +
Subtotal (95% CI)		**50**		**50**	**100.0%**	**1.00 [0.14 , 7.39]**		
Total events:	2		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.4. Comparison 5: Etidronate 400 mg/day versus placebo - subgroup of 4-year studies, Outcome 4: Radiographic vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
5.4.1 Radiographic vertebral fractures, secondary								
Lyritis 1997	4	39	9	35	66.1%	0.40 [0.13 , 1.18]		? ? − + − + +
Wimalawansa 1998	3	17	5	18	33.9%	0.64 [0.18 , 2.26]		+ ? − + + + +
Subtotal (95% CI)		**56**		**53**	**100.0%**	**0.48 [0.21 , 1.09]**		
Total events:	7		14					
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%								
Test for overall effect: Z = 1.76 (P = 0.08)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

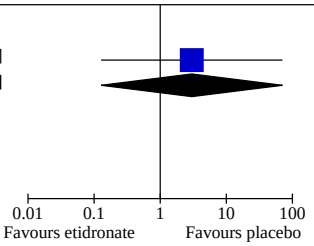
Comparison 6. Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Clinical vertebral fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1.1 Clinical vertebral fractures, primary	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.53]
6.2 Non-vertebral fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.2.1 Non-vertebral fractures, primary	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.2 Non-vertebral fractures, secondary	3	524	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.75, 1.73]
6.3 Hip fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.3.1 Hip fractures, secondary	1	209	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.12, 72.12]
6.4 Wrist fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.4.1 Wrist fractures, secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.5 Radiographic vertebral fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.5.1 Radiographic vertebral fractures, primary	1	152	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.5.2 Radiographic vertebral fractures, secondary	2	413	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.24, 0.96]

Analysis 6.1. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 1: Clinical vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Clinical vertebral fractures, primary						
Meunier 1997	1	27	0	27	100.0%	3.00 [0.13 , 70.53]
Subtotal (95% CI)		**27**		**27**	**100.0%**	**3.00 [0.13 , 70.53]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



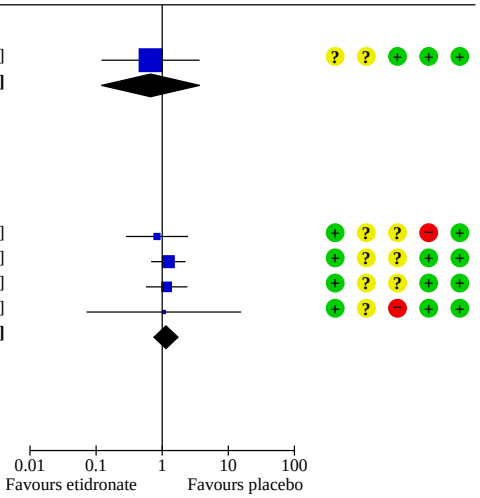
Risk of Bias: A ? B ? C + D + E +

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 6.2. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 2: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 Non-vertebral fractures, primary						
Meunier 1997	2	27	3	27	100.0%	0.67 [0.12 , 3.68]
Subtotal (95% CI)		**27**		**27**	**100.0%**	**0.67 [0.12 , 3.68]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
6.2.2 Non-vertebral fractures, secondary						
Storm 1990	5	33	6	33	17.1%	0.83 [0.28 , 2.46]
Watts 1990	20	105	16	104	45.9%	1.24 [0.68 , 2.25]
Watts 1990 (1)	14	107	12	107	34.2%	1.17 [0.57 , 2.40]
Wimalawansa 1998	1	17	1	18	2.8%	1.06 [0.07 , 15.62]
Subtotal (95% CI)		**262**		**262**	**100.0%**	**1.14 [0.75 , 1.73]**
Total events:	40		35			
Heterogeneity: Chi² = 0.40, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						

Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%



Footnotes

(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

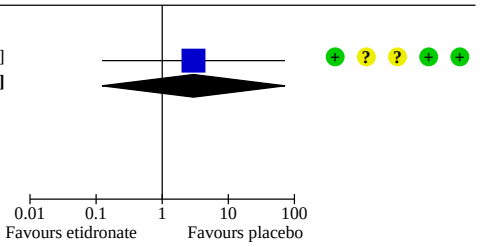
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 6.3. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 3: Hip fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Hip fractures, secondary						
Watts 1990	1	105	0	104	100.0%	2.97 [0.12 , 72.12]
Subtotal (95% CI)		**105**		**104**	**100.0%**	**2.97 [0.12 , 72.12]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						

Test for subgroup differences: Not applicable

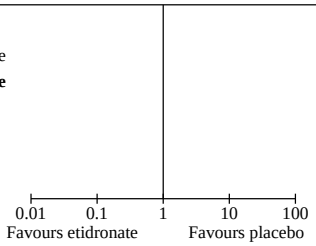


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 6.4. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 4: Wrist fractures

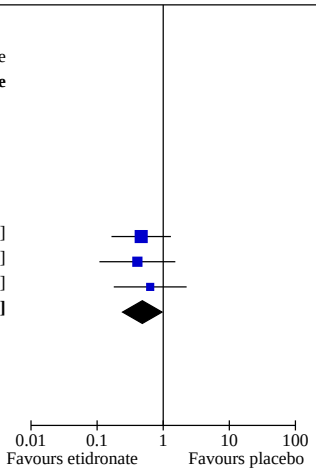
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
6.4.1 Wrist fractures, secondary							
Storm 1990	0	33	0	33		Not estimable	+ ? ? − +
Subtotal (95% CI)		**33**		**33**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 6.5. Comparison 6: Etidronate 400 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 5: Radiographic vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
6.5.1 Radiographic vertebral fractures, primary							
Herd 1997	0	75	0	77		Not estimable	? ? ? + +
Subtotal (95% CI)		**75**		**77**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.5.2 Radiographic vertebral fractures, secondary							
Watts 1990	5	98	10	91	46.3%	0.46 [0.16 , 1.31]	+ ? ? + +
Watts 1990 (1)	3	97	7	92	32.1%	0.41 [0.11 , 1.52]	+ ? ? + +
Wimalawansa 1998	3	17	5	18	21.7%	0.64 [0.18 , 2.26]	+ ? − + +
Subtotal (95% CI)		**212**		**201**	**100.0%**	**0.48 [0.24 , 0.96]**	
Total events:	11		22				
Heterogeneity: Chi² = 0.25, df = 2 (P = 0.88); I² = 0%							
Test for overall effect: Z = 2.08 (P = 0.04)							
Test for subgroup differences: Not applicable							



Footnotes
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

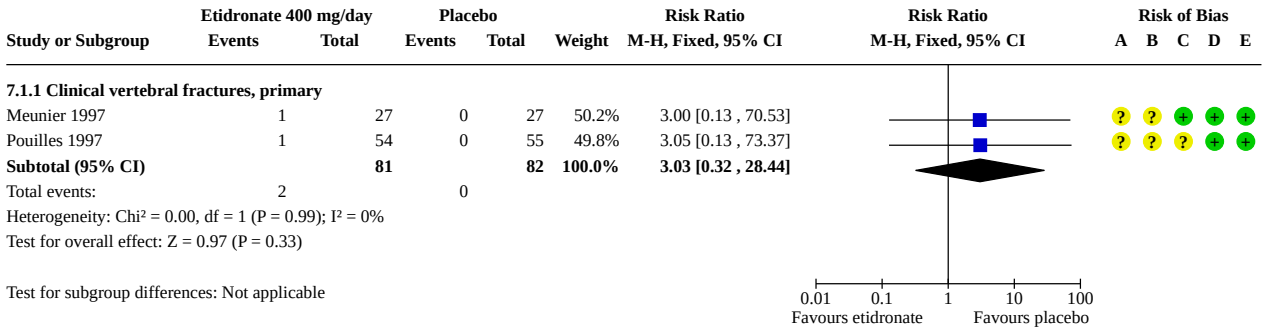
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 7. Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Clinical vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1.1 Clinical vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.44]
7.2 Non-vertebral fractures	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.2.1 Non-vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.61]
7.2.2 Non-vertebral fractures, secondary	4	624	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.60]
7.3 Hip fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.3.1 Hip fractures, primary	2	189	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3.2 Hip fractures, secondary	2	309	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.18, 5.66]
7.4 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.4.1 Wrist fractures, secondary	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.82]
7.5 Radiographic vertebral fractures	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.5.1 Radiographic vertebral fractures, primary	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
7.5.2 Radiographic vertebral fractures, secondary	3	558	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.27, 0.87]

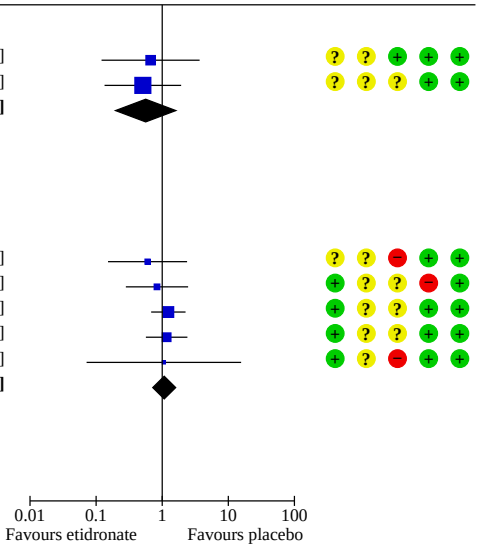
Analysis 7.1. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 1: Clinical vertebral fractures



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 7.2. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 2: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Non-vertebral fractures, primary						
Meunier 1997	2	27	3	27	33.5%	0.67 [0.12 , 3.68]
Pouilles 1997	3	54	6	55	66.5%	0.51 [0.13 , 1.93]
Subtotal (95% CI)		**81**		**82**	**100.0%**	**0.56 [0.20 , 1.61]**
Total events:	5		9			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
7.2.2 Non-vertebral fractures, secondary						
Lyritis 1997	3	50	5	50	12.5%	0.60 [0.15 , 2.38]
Storm 1990	5	33	6	33	15.0%	0.83 [0.28 , 2.46]
Watts 1990	20	105	16	104	40.1%	1.24 [0.68 , 2.25]
Watts 1990 (1)	14	107	12	107	30.0%	1.17 [0.57 , 2.40]
Wimalawansa 1998	1	17	1	18	2.4%	1.06 [0.07 , 15.62]
Subtotal (95% CI)		**312**		**312**	**100.0%**	**1.07 [0.72 , 1.60]**
Total events:	43		40			
Heterogeneity: Chi² = 1.16, df = 4 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.3%						



Footnotes

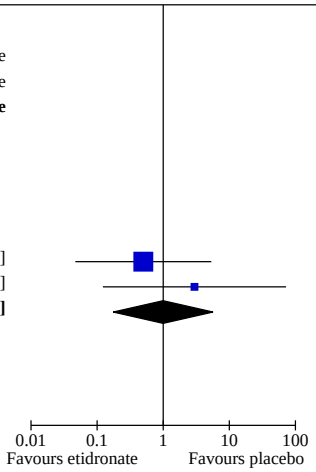
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

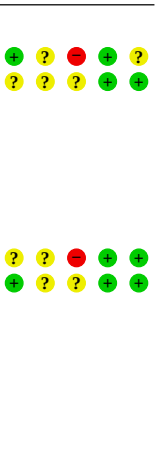
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 7.3. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 3: Hip fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.3.1 Hip fractures, primary						
Montessori 1997	0	40	0	40		Not estimable
Pouilles 1997	0	54	0	55		Not estimable
Subtotal (95% CI)		**94**		**95**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.3.2 Hip fractures, secondary						
Lyritis 1997	1	50	2	50	79.9%	0.50 [0.05 , 5.34]
Watts 1990	1	105	0	104	20.1%	2.97 [0.12 , 72.12]
Subtotal (95% CI)		**155**		**154**	**100.0%**	**1.00 [0.18 , 5.66]**
Total events:	2		2			
Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						

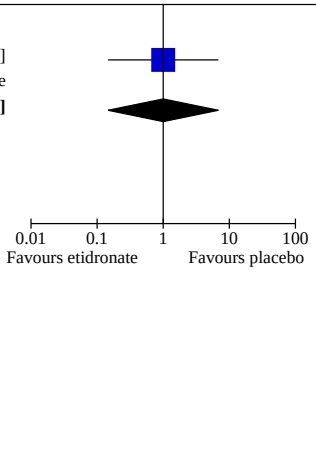




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

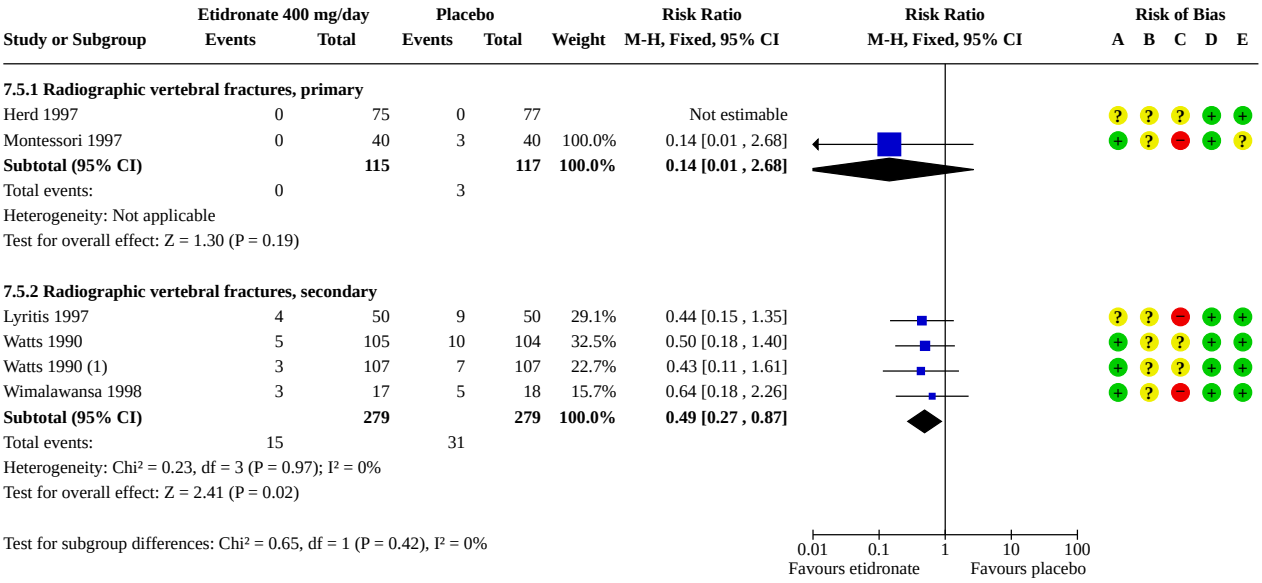
Analysis 7.4. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 4: Wrist fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.4.1 Wrist fractures, secondary						
Lyritis 1997	2	50	2	50	100.0%	1.00 [0.15 , 6.82]
Storm 1990	0	33	0	33		Not estimable
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.00 [0.15 , 6.82]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 7.5. Comparison 7: Etidronate 400 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 5: Radiographic vertebral fractures



Footnotes

(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 8. Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Non-vertebral fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1.1 Non-vertebral fractures, secondary	4	624	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.60]
8.2 Hip fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.2.1 Hip fractures, primary	1	80	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2.2 Hip fractures, secondary	2	309	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.18, 5.66]
8.3 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.3.1 Wrist fractures, secondary	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.82]
8.4 Radiographic vertebral fractures	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.4.1 Radiographic vertebral fractures, primary	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.4.2 Radiographic vertebral fractures, secondary	3	487	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.26, 0.82]

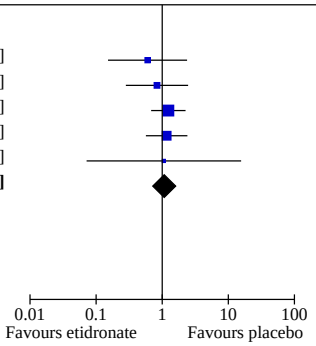
Analysis 8.1. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 1: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
8.1.1 Non-vertebral fractures, secondary											
Lyritis 1997	3	50	5	50	12.5%	0.60 [0.15 , 2.38]	?	?	−	+	+
Storm 1990	5	33	6	33	15.0%	0.83 [0.28 , 2.46]	+	?	?	−	+
Watts 1990	20	105	16	104	40.1%	1.24 [0.68 , 2.25]	+	?	?	+	+
Watts 1990 (1)	14	107	12	107	30.0%	1.17 [0.57 , 2.40]	+	?	?	+	+
Wimalawansa 1998	1	17	1	18	2.4%	1.06 [0.07 , 15.62]	+	?	−	+	+
Subtotal (95% CI)		**312**		**312**	**100.0%**	**1.07 [0.72 , 1.60]**					
Total events:	43		40								

Heterogeneity: Chi² = 1.16, df = 4 (P = 0.88); I² = 0%

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable



Footnotes

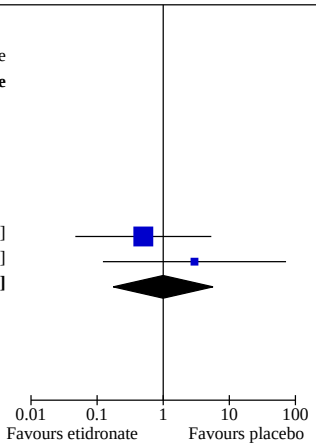
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 8.2. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 2: Hip fractures

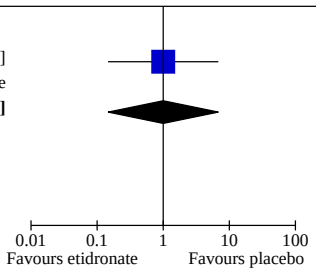
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
8.2.1 Hip fractures, primary							
Montessori 1997	0	40	0	40		Not estimable	+ ? − + ?
Subtotal (95% CI)		**40**		**40**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
8.2.2 Hip fractures, secondary							
Lyritis 1997	1	50	2	50	79.9%	0.50 [0.05 , 5.34]	? ? − + +
Watts 1990	1	105	0	104	20.1%	2.97 [0.12 , 72.12]	+ ? ? + +
Subtotal (95% CI)		**155**		**154**	**100.0%**	**1.00 [0.18 , 5.66]**	
Total events:	2		2				
Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

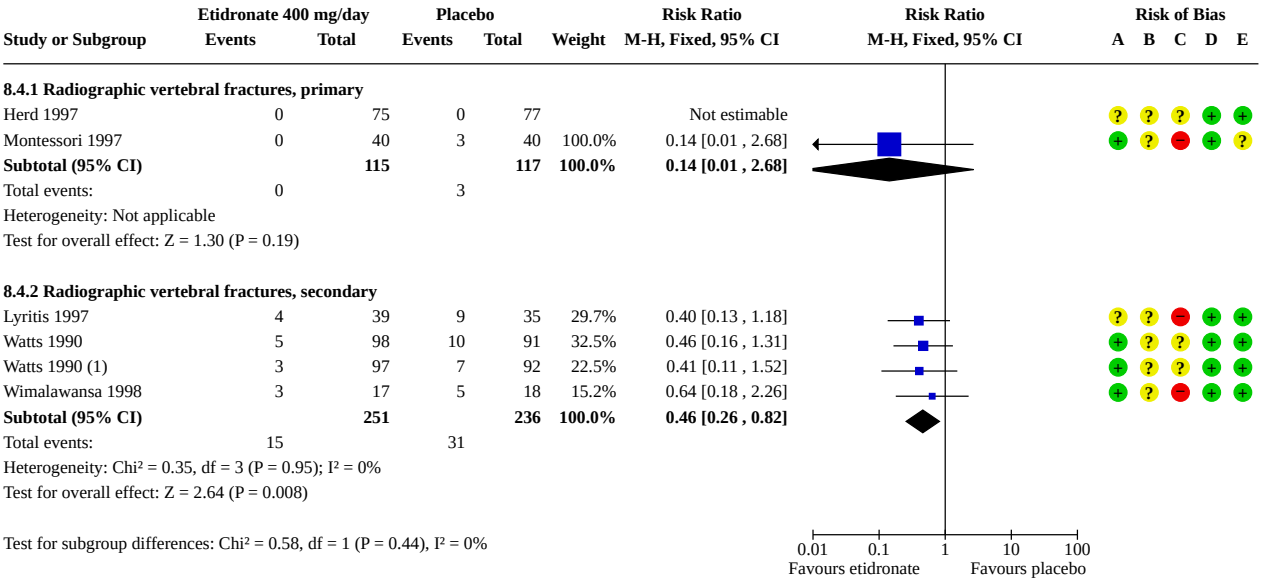
Analysis 8.3. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 3: Wrist fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
8.3.1 Wrist fractures, secondary							
Lyritis 1997	2	50	2	50	100.0%	1.00 [0.15 , 6.82]	? ? − + +
Storm 1990	0	33	0	33		Not estimable	+ ? ? − +
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.00 [0.15 , 6.82]**	
Total events:	2		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 8.4. Comparison 8: Etidronate 400 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 4: Radiographic vertebral fractures



Footnotes

(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 9. Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Clinical vertebral fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1.1 Clinical vertebral fractures, primary	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.53]
9.2 Non-vertebral fractures	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.2.1 Non-vertebral fractures, primary	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.68]
9.2.2 Non-vertebral fractures, secondary	4	624	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.60]
9.3 Hip fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.3.1 Hip fractures, secondary	2	309	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.18, 5.66]
9.4 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.4.1 Wrist fractures, secondary	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.5 Radiographic vertebral fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.5.1 Radiographic vertebral fractures, primary	1	152	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.5.2 Radiographic vertebral fractures, secondary	3	487	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.26, 0.82]

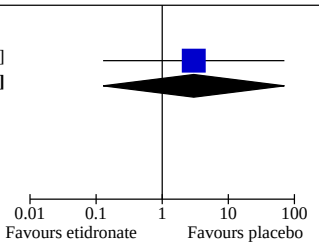
Analysis 9.1. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 1: Clinical vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 Clinical vertebral fractures, primary						
Meunier 1997	1	27	0	27	100.0%	3.00 [0.13 , 70.53]
Subtotal (95% CI)		**27**		**27**	**100.0%**	**3.00 [0.13 , 70.53]**
Total events:	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable



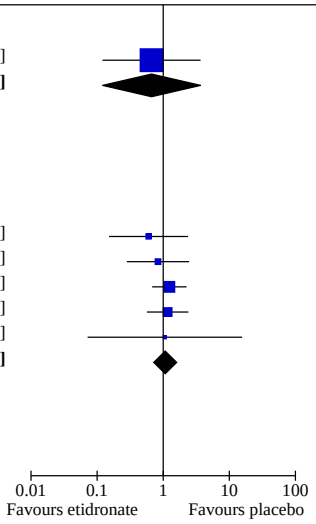
Risk of Bias: A ? B ? C + D + E +

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 9.2. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 2: Non-vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
9.2.1 Non-vertebral fractures, primary							
Meunier 1997	2	27	3	27	100.0%	0.67 [0.12 , 3.68]	? ? + + +
Subtotal (95% CI)		**27**		**27**	**100.0%**	**0.67 [0.12 , 3.68]**	
Total events:	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							
9.2.2 Non-vertebral fractures, secondary							
Lyritis 1997	3	50	5	50	12.5%	0.60 [0.15 , 2.38]	? ? − + +
Storm 1990	5	33	6	33	15.0%	0.83 [0.28 , 2.46]	+ ? ? − +
Watts 1990	20	105	16	104	40.1%	1.24 [0.68 , 2.25]	+ ? ? + +
Watts 1990 (1)	14	107	12	107	30.0%	1.17 [0.57 , 2.40]	+ ? ? + +
Wimalawansa 1998	1	17	1	18	2.4%	1.06 [0.07 , 15.62]	+ ? − + +
Subtotal (95% CI)		**312**		**312**	**100.0%**	**1.07 [0.72 , 1.60]**	
Total events:	43		40				
Heterogeneity: Chi² = 1.16, df = 4 (P = 0.88); I² = 0%							
Test for overall effect: Z = 0.34 (P = 0.73)							
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%							



Footnotes

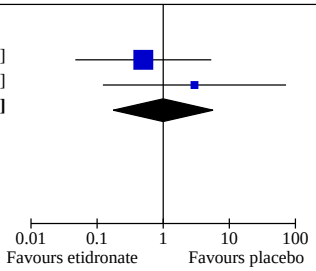
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 9.3. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 3: Hip fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
9.3.1 Hip fractures, secondary							
Lyritis 1997	1	50	2	50	79.9%	0.50 [0.05 , 5.34]	? ? − + +
Watts 1990	1	105	0	104	20.1%	2.97 [0.12 , 72.12]	+ ? ? + +
Subtotal (95% CI)		**155**		**154**	**100.0%**	**1.00 [0.18 , 5.66]**	
Total events:	2		2				
Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Not applicable							

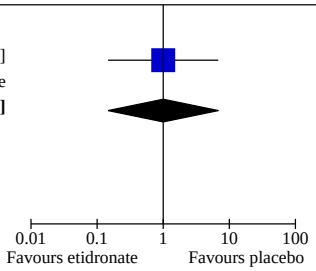


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 9.4. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 4: Wrist fractures

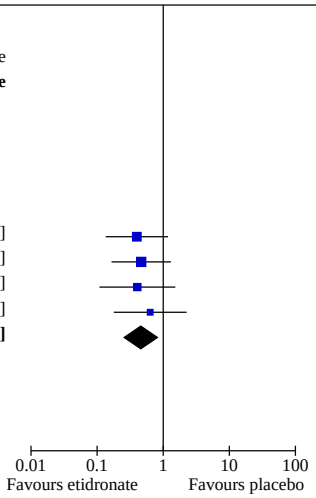
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
9.4.1 Wrist fractures, secondary											
Lyritis 1997	2	50	2	50	100.0%	1.00 [0.15 , 6.82]	?	?	−	+	+
Storm 1990	0	33	0	33		Not estimable	+	?	?	−	+
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.00 [0.15 , 6.82]**					
Total events:	2		2								
Heterogeneity: Not applicable											
Test for overall effect: Z = 0.00 (P = 1.00)											
Test for subgroup differences: Not applicable											



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 9.5. Comparison 9: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding primary/secondary studies defined by age alone, Outcome 5: Radiographic vertebral fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
9.5.1 Radiographic vertebral fractures, primary											
Herd 1997	0	75	0	77		Not estimable	?	?	?	+	+
Subtotal (95% CI)		**75**		**77**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
9.5.2 Radiographic vertebral fractures, secondary											
Lyritis 1997	4	39	9	35	29.7%	0.40 [0.13 , 1.18]	?	?	−	+	+
Watts 1990	5	98	10	91	32.5%	0.46 [0.16 , 1.31]	+	?	?	+	+
Watts 1990 (1)	3	97	7	92	22.5%	0.41 [0.11 , 1.52]	+	?	?	+	+
Wimalawansa 1998	3	17	5	18	15.2%	0.64 [0.18 , 2.26]	+	?	−	+	+
Subtotal (95% CI)		**251**		**236**	**100.0%**	**0.46 [0.26 , 0.82]**					
Total events:	15		31								
Heterogeneity: Chi² = 0.35, df = 3 (P = 0.95); I² = 0%											
Test for overall effect: Z = 2.64 (P = 0.008)											
Test for subgroup differences: Not applicable											



Footnotes
(1) Both etidronate 400 mg/day and placebo were used in ADFR regimen.

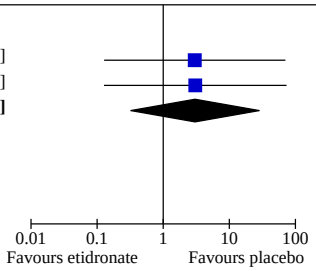
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 10. Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Clinical vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1.1 Clinical vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.44]
10.2 Non-vertebral fractures	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.2.1 Non-vertebral fractures, primary	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.61]
10.2.2 Non-vertebral fractures, secondary	3	310	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.67, 1.88]
10.3 Hip fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.3.1 Hip fractures, primary	2	189	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.3.2 Hip fractures, secondary	1	209	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.12, 72.12]
10.4 Wrist fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.4.1 Wrist fractures, secondary	1	66	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.5 Radiographic vertebral fractures	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.5.1 Radiographic vertebral fractures, primary	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
10.5.2 Radiographic vertebral fractures, secondary	2	224	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.23, 1.16]

Analysis 10.1. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 1: Clinical vertebral fractures

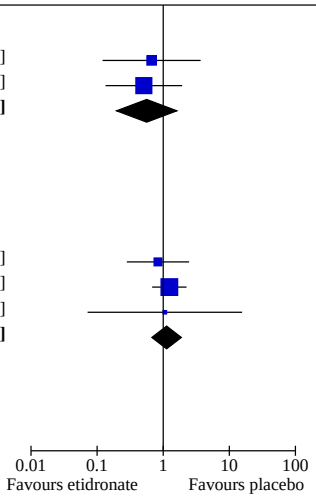
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
10.1.1 Clinical vertebral fractures, primary							
Meunier 1997	1	27	0	27	50.2%	3.00 [0.13 , 70.53]	? ? + + +
Pouilles 1997	1	54	0	55	49.8%	3.05 [0.13 , 73.37]	? ? ? + +
Subtotal (95% CI)		**81**		**82**	**100.0%**	**3.03 [0.32 , 28.44]**	
Total events:	2		0				
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.97 (P = 0.33)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 10.2. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 2: Non-vertebral fractures

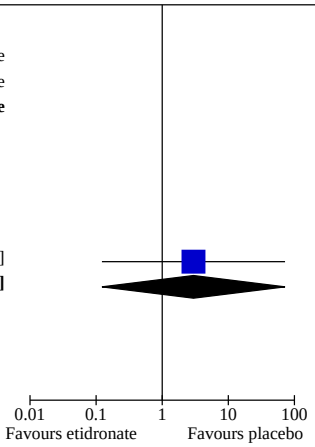
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
10.2.1 Non-vertebral fractures, primary							
Meunier 1997	2	27	3	27	33.5%	0.67 [0.12 , 3.68]	? ? + + +
Pouilles 1997	3	54	6	55	66.5%	0.51 [0.13 , 1.93]	? ? ? + +
Subtotal (95% CI)		**81**		**82**	**100.0%**	**0.56 [0.20 , 1.61]**	
Total events:	5		9				
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%							
Test for overall effect: Z = 1.08 (P = 0.28)							
10.2.2 Non-vertebral fractures, secondary							
Storm 1990	5	33	6	33	26.0%	0.83 [0.28 , 2.46]	+ ? ? − +
Watts 1990	20	105	16	104	69.8%	1.24 [0.68 , 2.25]	+ ? ? + +
Wimalawansa 1998	1	17	1	18	4.2%	1.06 [0.07 , 15.62]	+ ? − + +
Subtotal (95% CI)		**155**		**155**	**100.0%**	**1.13 [0.67 , 1.88]**	
Total events:	26		23				
Heterogeneity: Chi² = 0.39, df = 2 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.45 (P = 0.65)							
Test for subgroup differences: Chi² = 1.36, df = 1 (P = 0.24), I² = 26.3%							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 10.3. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 3: Hip fractures

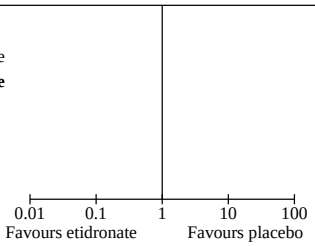
Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
10.3.1 Hip fractures, primary							
Montessori 1997	0	40	0	40		Not estimable	+ ? − + ?
Pouilles 1997	0	54	0	55		Not estimable	? ? ? + +
Subtotal (95% CI)		**94**		**95**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
10.3.2 Hip fractures, secondary							
Watts 1990	1	105	0	104	100.0%	2.97 [0.12 , 72.12]	+ ? ? + +
Subtotal (95% CI)		**105**		**104**	**100.0%**	**2.97 [0.12 , 72.12]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

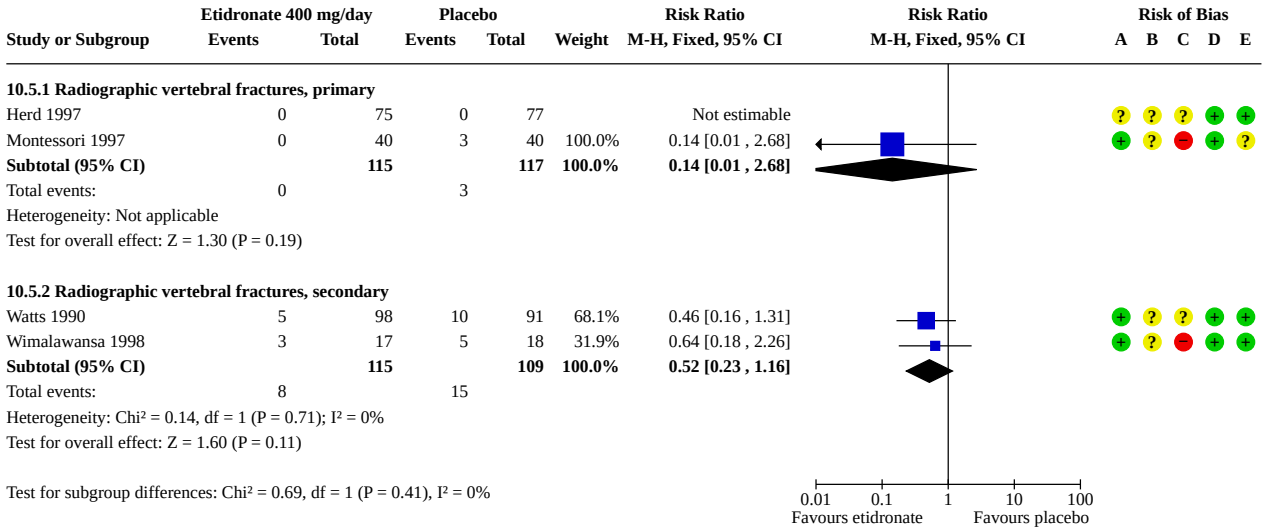
Analysis 10.4. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 4: Wrist fractures

Study or Subgroup	Etidronate 400 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
10.4.1 Wrist fractures, secondary							
Storm 1990	0	33	0	33		Not estimable	+ ? ? − +
Subtotal (95% CI)		**33**		**33**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 10.5. Comparison 10: Etidronate 400 mg/day versus placebo - sensitivity analyses excluding studies applying an ADFR regimen, Outcome 5: Radiographic vertebral fractures



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

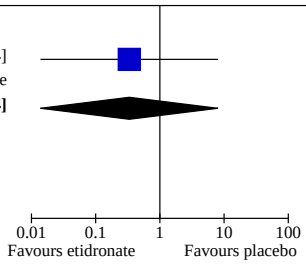
Comparison 11. Etidronate 200 mg/day versus placebo - base case analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Hip fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1.1 Hip fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
11.2 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.2.1 Wrist fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3 Radiographic vertebral fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.3.1 Radiographic vertebral fractures, secondary	3	221	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.17, 0.60]
11.4 Withdrawals due to adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.4.1 Withdrawals due to adverse events, secondary	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]
11.5 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.5.2 Serious adverse events, secondary	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.6 Gastrointestinal adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.6.1 Gastrointestinal adverse events, secondary	1	49	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [0.51, 11.21]
11.7 Atypical femoral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.7.2 Atypical femoral fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 11.1. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 1: Hip fractures

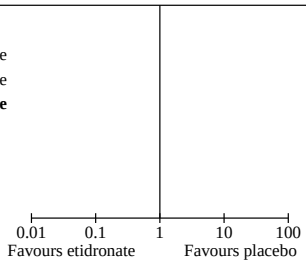
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
11.1.1 Hip fractures, secondary							
Ishida 2004	0	66	1	66	100.0%	0.33 [0.01 , 8.04]	+ ? − + + ? −
Iwamoto 2001	0	25	0	24		Not estimable	? ? − + ? + −
Subtotal (95% CI)		**91**		**90**	**100.0%**	**0.33 [0.01 , 8.04]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 11.2. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 2: Wrist fractures

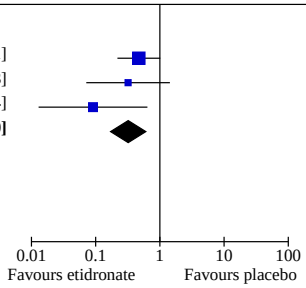
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
11.2.1 Wrist fractures, secondary							
Ishida 2004	0	66	0	66		Not estimable	+ ? − + + ? −
Iwamoto 2001	0	25	0	24		Not estimable	? ? − + ? + −
Subtotal (95% CI)		**91**		**90**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 11.3. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 3: Radiographic vertebral fractures

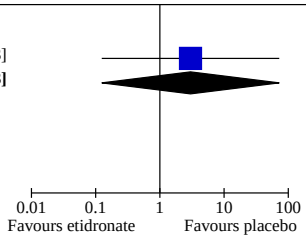
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
11.3.1 Radiographic vertebral fractures, secondary								
Ishida 2004	8	66	17	66	49.8%	0.47 [0.22 , 1.01]		+ ? − + + ? −
Iwamoto 2001	2	25	6	24	17.9%	0.32 [0.07 , 1.43]		? ? − + ? + −
Shiota 2001	1	20	11	20	32.2%	0.09 [0.01 , 0.64]		? ? − + ? + +
Subtotal (95% CI)		**111**		**110**	**100.0%**	**0.32 [0.17 , 0.60]**		
Total events:	11		34					
Heterogeneity: Chi² = 2.56, df = 2 (P = 0.28); I² = 22%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 11.4. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 4: Withdrawals due to adverse events

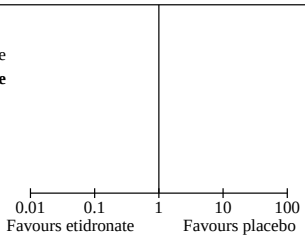
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
11.4.1 Withdrawals due to adverse events, secondary								
Ishida 2004	1	66	0	66	100.0%	3.00 [0.12 , 72.33]		+ ? − − + ? −
Subtotal (95% CI)		**66**		**66**	**100.0%**	**3.00 [0.12 , 72.33]**		
Total events:	1		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 11.5. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 5: Serious adverse events

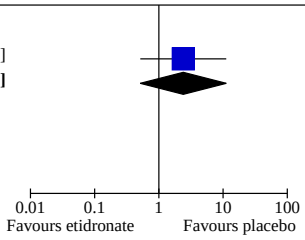
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
11.5.2 Serious adverse events, secondary								
Shiota 2001	0	20	0	20		Not estimable		? ? − − ? + +
Subtotal (95% CI)		**20**		**20**		**Not estimable**		
Total events:	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

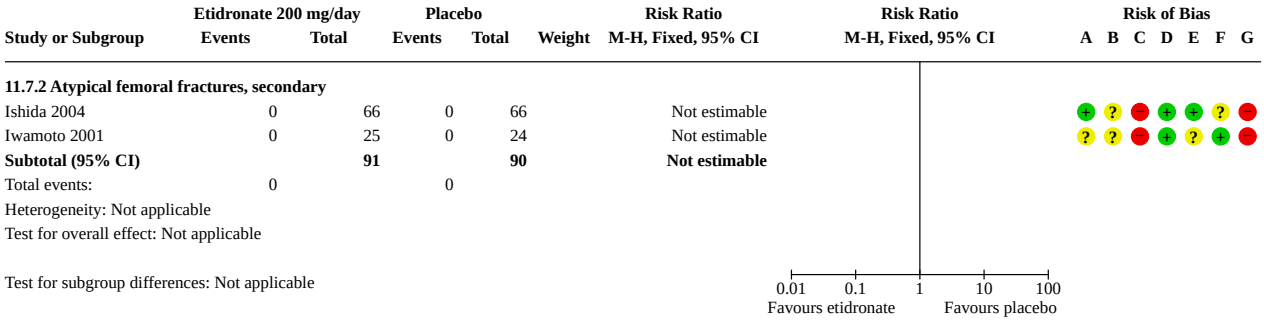
Analysis 11.6. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 6: Gastrointestinal adverse events

Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
11.6.1 Gastrointestinal adverse events, secondary								
Iwamoto 2001	5	25	2	24	100.0%	2.40 [0.51 , 11.21]		? ? − − ? + −
Subtotal (95% CI)		**25**		**24**	**100.0%**	**2.40 [0.51 , 11.21]**		
Total events:	5		2					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 11.7. Comparison 11: Etidronate 200 mg/day versus placebo - base case analysis, Outcome 7: Atypical femoral fractures

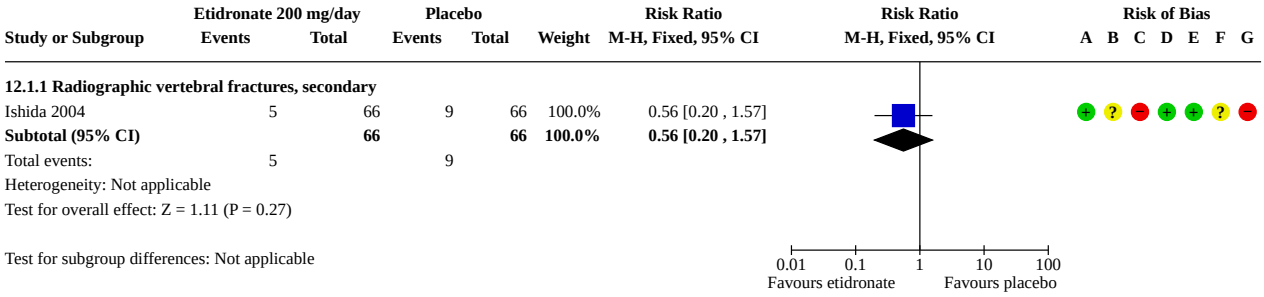


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Safety outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 12. Etidronate 200 mg/day versus placebo - subgroup of 1-year studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Radiographic vertebral fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1.1 Radiographic vertebral fractures, secondary	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.57]

Analysis 12.1. Comparison 12: Etidronate 200 mg/day versus placebo - subgroup of 1-year studies, Outcome 1: Radiographic vertebral fractures



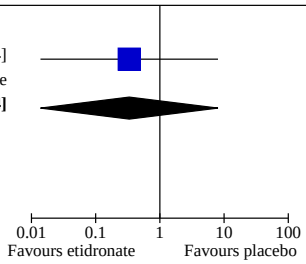
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 13. Etidronate 200 mg/day versus placebo - subgroup of 2-year studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Hip fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1.1 Hip fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
13.2 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.2.1 Wrist fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.3 Radiographic vertebral fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.3.1 Radiographic vertebral fractures, secondary	3	221	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.17, 0.60]

Analysis 13.1. Comparison 13: Etidronate 200 mg/day versus placebo - subgroup of 2-year studies, Outcome 1: Hip fractures

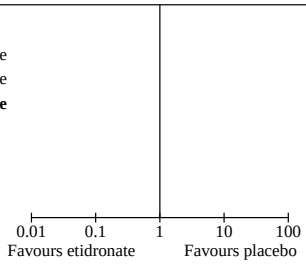
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.1.1 Hip fractures, secondary						
Ishida 2004	0	66	1	66	100.0%	0.33 [0.01 , 8.04]
Iwamoto 2001	0	25	0	24		Not estimable
Subtotal (95% CI)		**91**		**90**	**100.0%**	**0.33 [0.01 , 8.04]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 13.2. Comparison 13: Etidronate 200 mg/day versus placebo - subgroup of 2-year studies, Outcome 2: Wrist fractures

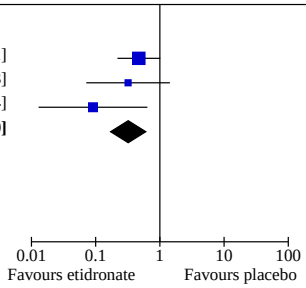
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
13.2.1 Wrist fractures, secondary							
Ishida 2004	0	66	0	66		Not estimable	+ ? − + + ? −
Iwamoto 2001	0	25	0	24		Not estimable	? ? − + ? + −
Subtotal (95% CI)		**91**		**90**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 13.3. Comparison 13: Etidronate 200 mg/day versus placebo - subgroup of 2-year studies, Outcome 3: Radiographic vertebral fractures

Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
13.3.1 Radiographic vertebral fractures, secondary							
Ishida 2004	8	66	17	66	49.8%	0.47 [0.22 , 1.01]	+ ? − + + ? −
Iwamoto 2001	2	25	6	24	17.9%	0.32 [0.07 , 1.43]	? ? − + ? + −
Shiota 2001	1	20	11	20	32.2%	0.09 [0.01 , 0.64]	? ? − + ? + +
Subtotal (95% CI)		**111**		**110**	**100.0%**	**0.32 [0.17 , 0.60]**	
Total events:	11		34				
Heterogeneity: Chi² = 2.56, df = 2 (P = 0.28); I² = 22%							
Test for overall effect: Z = 3.53 (P = 0.0004)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Efficacy outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

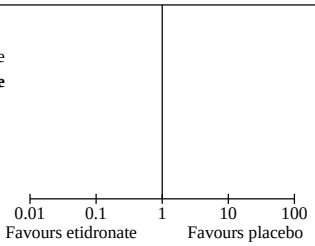
Comparison 14. Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Hip fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1.1 Hip fractures, secondary	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 Wrist fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.2.1 Wrist fractures, secondary	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3 Radiographic vertebral fractures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.3.1 Radiographic vertebral fractures, secondary	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.07, 1.43]

Analysis 14.1. Comparison 14: Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 1: Hip fractures

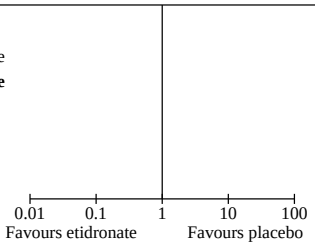
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
14.1.1 Hip fractures, secondary												
Iwamoto 2001	0	25	0	24		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**25**		**24**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

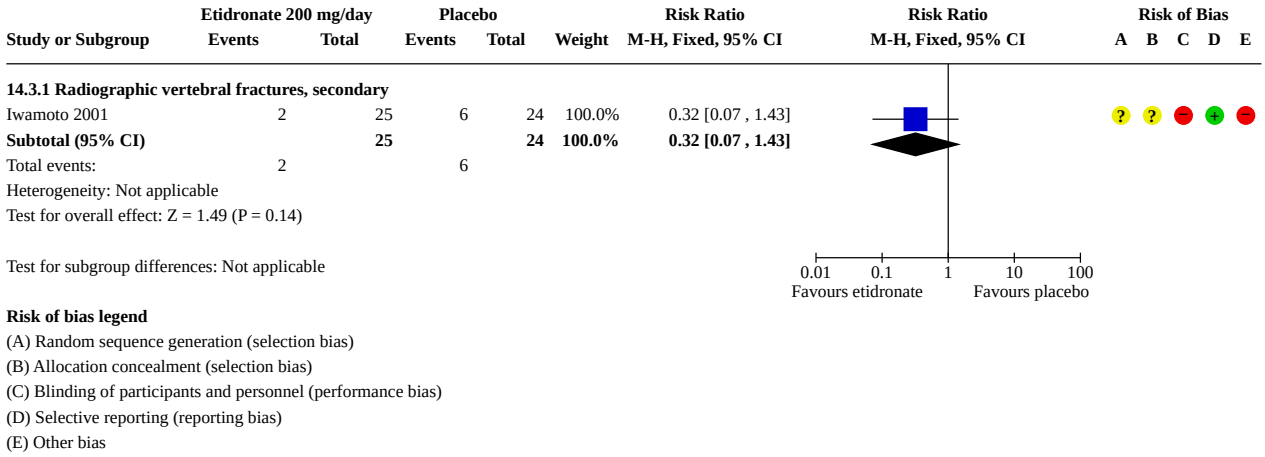
Analysis 14.2. Comparison 14: Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 2: Wrist fractures

Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
14.2.1 Wrist fractures, secondary												
Iwamoto 2001	0	25	0	24		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**25**		**24**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 14.3. Comparison 14: Etidronate 200 mg/day versus placebo - subgroup of bisphosphonate-naïve participants, Outcome 3: Radiographic vertebral fractures

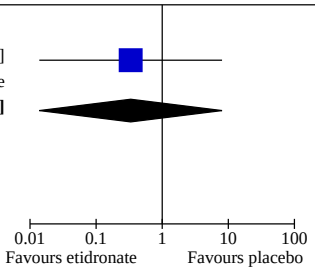


Comparison 15. Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Hip fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1.1 Hip fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
15.2 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.2.1 Wrist fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.3 Radiographic vertebral fractures	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.3.1 Radiographic vertebral fractures, secondary	3	221	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.17, 0.60]

Analysis 15.1. Comparison 15: Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 1: Hip fractures

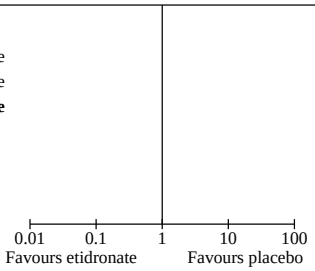
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
15.1.1 Hip fractures, secondary												
Ishida 2004	0	66	1	66	100.0%	0.33 [0.01 , 8.04]		+	?	−	?	−
Iwamoto 2001	0	25	0	24		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**91**		**90**	**100.0%**	**0.33 [0.01 , 8.04]**						
Total events:	0		1									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.68 (P = 0.50)												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

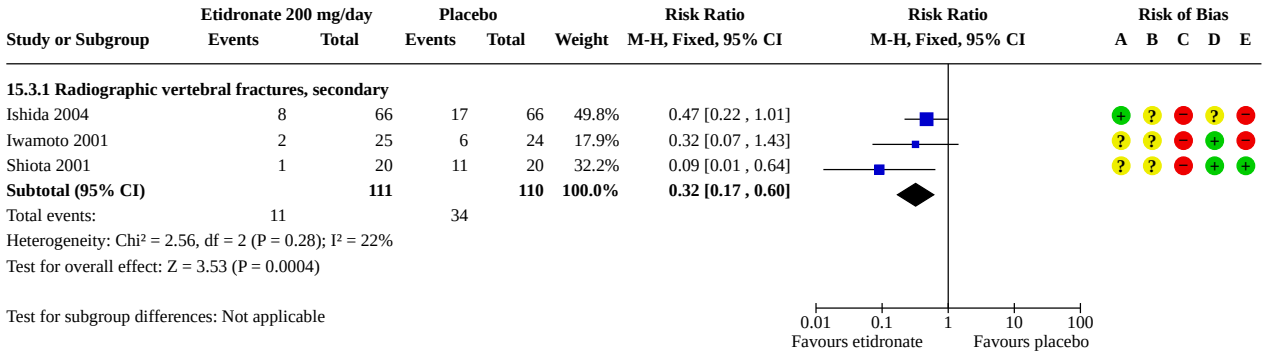
Analysis 15.2. Comparison 15: Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 2: Wrist fractures

Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
15.2.1 Wrist fractures, secondary												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Iwamoto 2001	0	25	0	24		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**91**		**90**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 15.3. Comparison 15: Etidronate 200 mg/day versus placebo - sensitivity analyses with baseline denominators, Outcome 3: Radiographic vertebral fractures



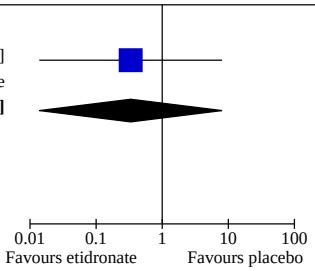
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 16. Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Hip fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1.1 Hip fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
16.2 Wrist fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.2.1 Wrist fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.3 Radiographic vertebral fractures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.3.1 Radiographic vertebral fractures, secondary	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.22, 0.85]

Analysis 16.1. Comparison 16: Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 1: Hip fractures

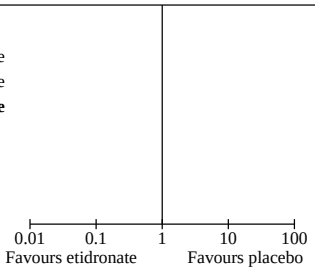
Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
16.1.1 Hip fractures, secondary							
Ishida 2004	0	66	1	66	100.0%	0.33 [0.01 , 8.04]	+ ? − ? −
Iwamoto 2001	0	25	0	24		Not estimable	? ? − + −
Subtotal (95% CI)		**91**		**90**	**100.0%**	**0.33 [0.01 , 8.04]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

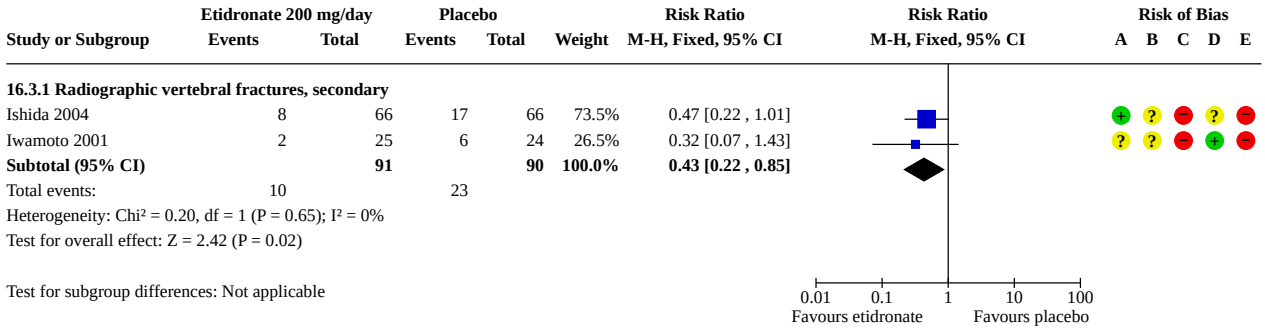
Analysis 16.2. Comparison 16: Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 2: Wrist fractures

Study or Subgroup	Etidronate 200 mg/day Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E
16.2.1 Wrist fractures, secondary							
Ishida 2004	0	66	0	66		Not estimable	+ ? − ? −
Iwamoto 2001	0	25	0	24		Not estimable	? ? − + −
Subtotal (95% CI)		**91**		**90**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 16.3. Comparison 16: Etidronate 200 mg/day versus placebo - sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 3: Radiographic vertebral fractures

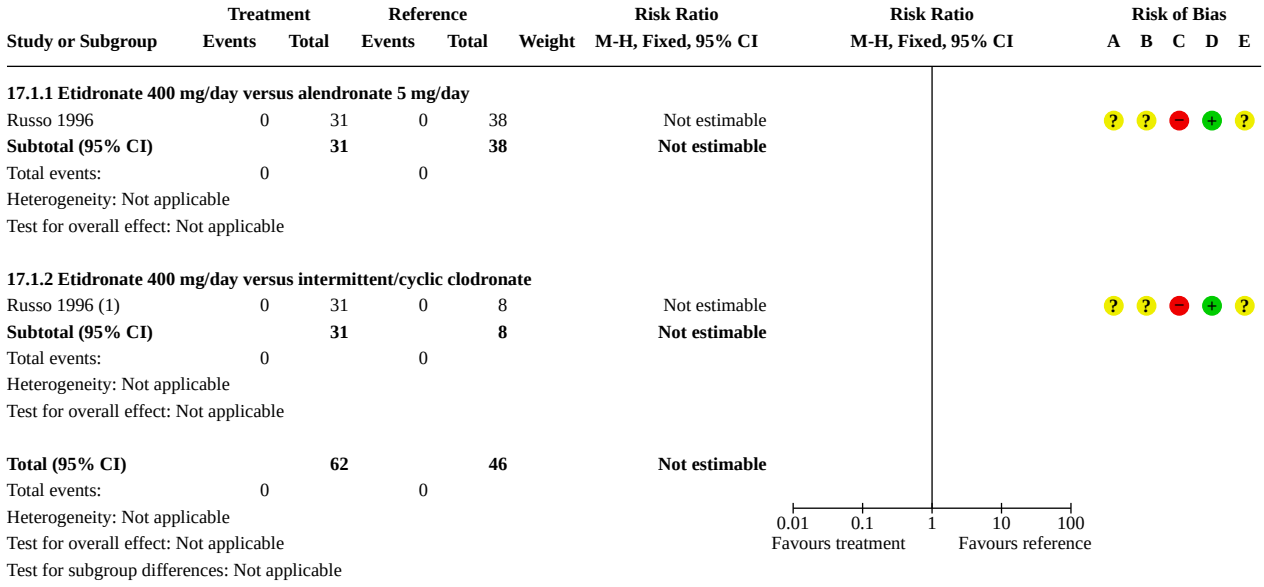


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 17. Clinical vertebral fractures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Treatment versus reference, secondary	1	108	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 17.1. Comparison 17: Clinical vertebral fractures, Outcome 1: Treatment versus reference, secondary



Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 18. Non-vertebral fractures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Treatment versus reference, secondary	6	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.49, 1.62]
18.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.1.3 Etidronate 400 mg/day versus fluoride 50 mg/day	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.23, 1.86]
18.1.4 Etidronate 400 mg/day versus HRT	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.07, 15.62]
18.1.5 Etidronate 400 mg/day versus etidronate 400 mg/day plus HRT	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.08, 16.52]
18.1.6 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

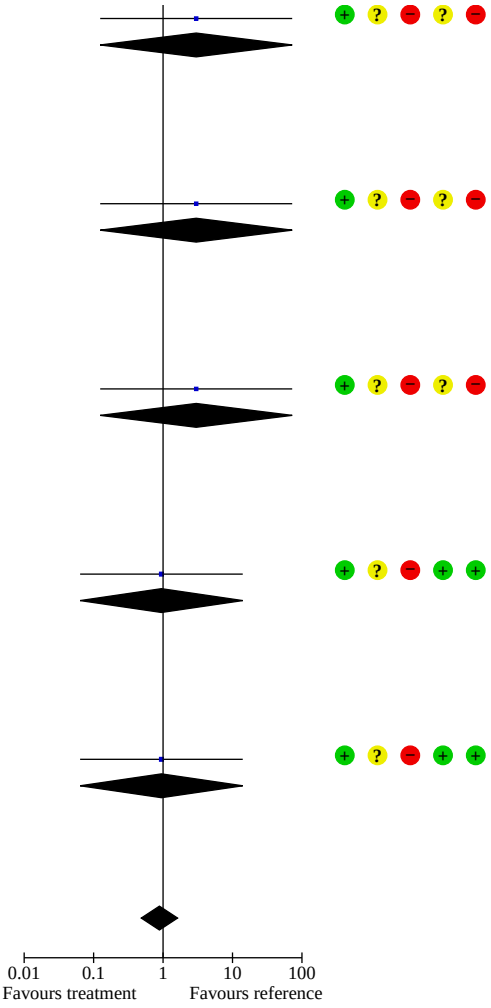
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1.7 Etidronate 200 mg/day versus risedronate 2.5 mg/day	1	235	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.17, 1.92]
18.1.8 Etidronate 200 mg/day versus alfacalcidol 1 µg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.65]
18.1.9 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]
18.1.10 Etidronate 200 mg/day versus HRT	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]
18.1.11 Etidronate 200 mg/day versus menatetrenone 45 mg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]
18.1.12 Etidronate 400 mg/day plus HRT versus placebo	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.06, 14.04]
18.1.13 Etidronate 400 mg/day plus HRT versus HRT	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.06, 14.04]

Analysis 18.1. Comparison 18: Non-vertebral fractures, Outcome 1: Treatment versus reference, secondary

Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
18.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day												
Russo 1996	0	31	0	38		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**38**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
18.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate												
Russo 1996 (1)	0	31	0	8		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**8**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
18.1.3 Etidronate 400 mg/day versus fluoride 50 mg/day												
Guañabens 2000	6	47	6	31	35.0%	0.66 [0.23 , 1.86]		?	?	−	+	+
Subtotal (95% CI)		**47**		**31**	**35.0%**	**0.66 [0.23 , 1.86]**						
Total events:	6		6									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.79 (P = 0.43)												
18.1.4 Etidronate 400 mg/day versus HRT												
Wimalawansa 1998 (2)	1	17	1	18	4.7%	1.06 [0.07 , 15.62]		+	?	−	+	+
Subtotal (95% CI)		**17**		**18**	**4.7%**	**1.06 [0.07 , 15.62]**						
Total events:	1		1									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.04 (P = 0.97)												
18.1.5 Etidronate 400 mg/day versus etidronate 400 mg/day plus HRT												
Wimalawansa 1998 (2)	1	17	1	19	4.6%	1.12 [0.08 , 16.52]		+	?	−	+	+
Subtotal (95% CI)		**17**		**19**	**4.6%**	**1.12 [0.08 , 16.52]**						
Total events:	1		1									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.08 (P = 0.94)												
18.1.6 Etidronate 200 mg/day versus alendronate 5 mg/day												
Iwamoto 2005	0	25	0	25		Not estimable		−	−	−	+	−
Subtotal (95% CI)		**25**		**25**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
18.1.7 Etidronate 200 mg/day versus risedronate 2.5 mg/day												
Fukunaga 2002	4	117	7	118	33.7%	0.58 [0.17 , 1.92]		?	?	+	+	+
Subtotal (95% CI)		**117**		**118**	**33.7%**	**0.58 [0.17 , 1.92]**						
Total events:	4		7									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.90 (P = 0.37)												
18.1.8 Etidronate 200 mg/day versus alfacalcidol 1 µg/day												
Ishida 2004	1	66	1	66	4.8%	1.00 [0.06 , 15.65]		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**	**4.8%**	**1.00 [0.06 , 15.65]**						
Total events:	1		1									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.00 (P = 1.00)												
18.1.9 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV												
Ishida 2004	1	66	0	66	2.4%	3.00 [0.12 , 72.33]		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**	**2.4%**	**3.00 [0.12 , 72.33]**						

Analysis 18.1. (Continued)

Ishida 2004	1	66	0	66	2.4%	3.00 [0.12 , 72.33]
Subtotal (95% CI)		**66**		**66**	**2.4%**	**3.00 [0.12 , 72.33]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
18.1.10 Etidronate 200 mg/day versus HRT						
Ishida 2004 (3)	1	66	0	66	2.4%	3.00 [0.12 , 72.33]
Subtotal (95% CI)		**66**		**66**	**2.4%**	**3.00 [0.12 , 72.33]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
18.1.11 Etidronate 200 mg/day versus menatetrenone 45 mg/day						
Ishida 2004	1	66	0	66	2.4%	3.00 [0.12 , 72.33]
Subtotal (95% CI)		**66**		**66**	**2.4%**	**3.00 [0.12 , 72.33]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
18.1.12 Etidronate 400 mg/day plus HRT versus placebo						
Wimalawansa 1998 (4)	1	19	1	18	5.0%	0.95 [0.06 , 14.04]
Subtotal (95% CI)		**19**		**18**	**5.0%**	**0.95 [0.06 , 14.04]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
18.1.13 Etidronate 400 mg/day plus HRT versus HRT						
Wimalawansa 1998 (4)	1	19	1	18	5.0%	0.95 [0.06 , 14.04]
Subtotal (95% CI)		**19**		**18**	**5.0%**	**0.95 [0.06 , 14.04]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
Total (95% CI)		**587**		**557**	**100.0%**	**0.89 [0.49 , 1.62]**
Total events:	18		18			
Heterogeneity: Chi² = 2.55, df = 9 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
Test for subgroup differences: Chi² = 2.53, df = 9 (P = 0.98), I² = 0%						



Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(2) HRT: Premarin 0.625 mg/day + norgestrel 150 µg/day] for 12 days per month
(3) HRT: conjugated estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day
(4) HRT: [Premarin 0.625 mg/day + norgestrel 150 µg/day] for 12 days per month

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 19. Hip fractures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Treatment versus reference, secondary	5	774	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

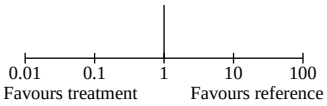
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.3 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.4 Etidronate 200 mg/day versus alfacalcidol 1 µg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.5 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.6 Etidronate 200 mg/day versus HRT	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.7 Etidronate 200 mg/day versus menatetrenone 45 mg/day	2	180	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1.8 Etidronate 200 mg/day versus etidronate 200 mg/day plus alfacalcidol 1 µg/day)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 19.1. Comparison 19: Hip fractures, Outcome 1: Treatment versus reference, secondary

Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
19.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day												
Russo 1996	0	31	0	38		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**38**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate												
Russo 1996 (1)	0	31	0	8		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**8**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.3 Etidronate 200 mg/day versus alendronate 5 mg/day												
Iwamoto 2005	0	25	0	25		Not estimable		−	−	−	+	−
Subtotal (95% CI)		**25**		**25**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.4 Etidronate 200 mg/day versus alfacalcidol 1 µg/day												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.5 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.6 Etidronate 200 mg/day versus HRT												
Ishida 2004 (2)	0	66	0	66		Not estimable		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.7 Etidronate 200 mg/day versus menatetrenone 45 mg/day												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Iwamoto 2001	0	25	0	23		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**91**		**89**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
19.1.8 Etidronate 200 mg/day versus etidronate 200 mg/day plus alfacalcidol 1 µg/day)												
Iwamoto 2003b	0	20	0	20		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**20**		**20**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Total (95% CI)		**396**		**378**		**Not estimable**						
Total events:	0		0									

Analysis 19.1. (Continued)

Total (95% CI)	**396**	**378**	**Not estimable**	
Total events:	0	0		
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
Test for subgroup differences: Not applicable				



Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(2) HRT: conjugated estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 20. Wrist fractures

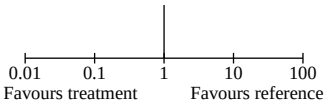
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Treatment versus reference, secondary	5	774	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.3 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.4 Etidronate 200 mg/day versus alfacalcidol 1 µg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.5 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.6 Etidronate 200 mg/day versus HRT	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.7 Etidronate 200 mg/day versus menatetrenone 45 mg/day	2	180	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.1.8 Etidronate 200 mg/day versus etidronate 200 mg/day plus alfacalcidol 1 µg/day	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 20.1. Comparison 20: Wrist fractures, Outcome 1: Treatment versus reference, secondary

Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
20.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day												
Russo 1996	0	31	0	38		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**38**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate												
Russo 1996 (1)	0	31	0	8		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**8**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.3 Etidronate 200 mg/day versus alendronate 5 mg/day												
Iwamoto 2005	0	25	0	25		Not estimable		−	−	−	+	−
Subtotal (95% CI)		**25**		**25**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.4 Etidronate 200 mg/day versus alfacalcidol 1 µg/day												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.5 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.6 Etidronate 200 mg/day versus HRT												
Ishida 2004 (2)	0	66	0	66		Not estimable		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.7 Etidronate 200 mg/day versus menatetrenone 45 mg/day												
Ishida 2004	0	66	0	66		Not estimable		+	?	−	?	−
Iwamoto 2001	0	25	0	23		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**91**		**89**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
20.1.8 Etidronate 200 mg/day versus etidronate 200 mg/day plus alfacalcidol 1 µg/day												
Iwamoto 2003b	0	20	0	20		Not estimable		?	?	−	+	−
Subtotal (95% CI)		**20**		**20**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
Total (95% CI)		**396**		**378**		**Not estimable**						
Total events:	0		0									

Analysis 20.1. (Continued)

Total (95% CI)	**396**	**378**	**Not estimable**	
Total events:	0	0		
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
Test for subgroup differences: Not applicable				



Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(2) HRT: conjugated estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 21. Radiographic vertebral fractures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Treatment versus reference, secondary	8	1204	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.35]
21.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.1.3 Etidronate 400 mg/day versus fluoride 50 mg/day	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.38, 2.93]
21.1.4 Etidronate 400 mg/day versus HRT	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.30, 8.37]
21.1.5 Etidronate 400 mg/day versus etidronate 400 mg/day plus HRT	1	36	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [0.38, 29.26]
21.1.6 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.1.7 Etidronate 200 mg/day versus risedronate 2.5 mg/day	1	207	Risk Ratio (M-H, Fixed, 95% CI)	4.77 [0.23, 98.08]
21.1.8 Etidronate 200 mg/day versus alfacalcidol 1 µg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.31, 1.69]
21.1.9 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.40, 2.51]
21.1.10 Etidronate 200 mg/day versus HRT	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.44, 2.97]
21.1.11 Etidronate 200 mg/day versus menatetrenone 45 mg/day	2	180	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.40, 2.00]

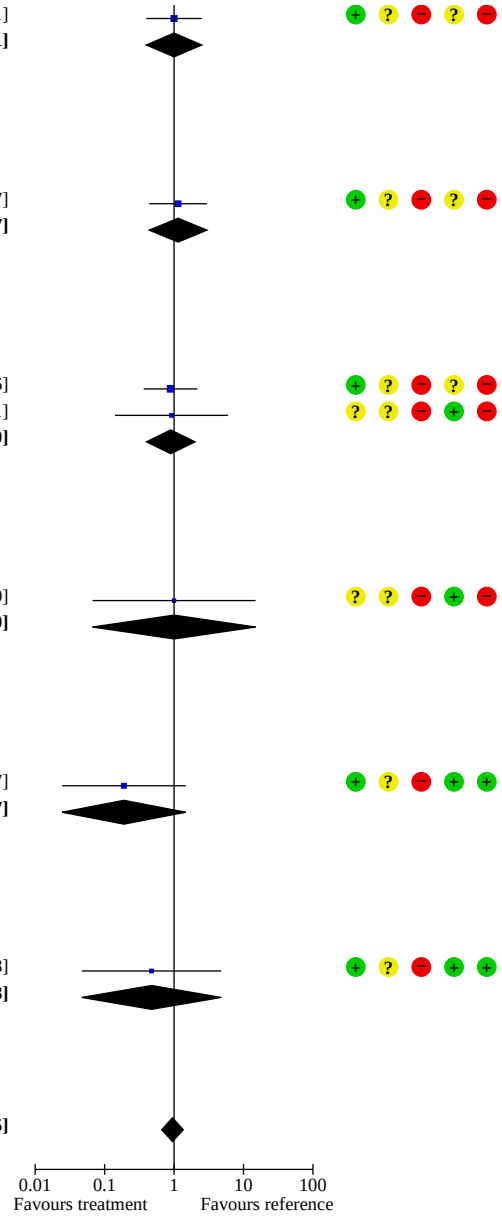
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1.12 Etidronate 200 mg/day versus etidronate 200 mg/day plus alfacalcidol 1 µg/day	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.07, 14.90]
21.1.13 Etidronate 400 mg/day plus HRT versus placebo	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.47]
21.1.14 Etidronate 400 mg/day plus HRT versus HRT	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.05, 4.78]

Analysis 21.1. Comparison 21: Radiographic vertebral fractures, Outcome 1: Treatment versus reference, secondary

Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
21.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day												
Russo 1996	0	31	0	38		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**38**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
21.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate												
Russo 1996 (1)	0	31	0	8		Not estimable		?	?	−	+	?
Subtotal (95% CI)		**31**		**8**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
21.1.3 Etidronate 400 mg/day versus fluoride 50 mg/day												
Guañabens 2000	8	47	5	31	11.0%	1.06 [0.38 , 2.93]		?	?	−	+	+
Subtotal (95% CI)		**47**		**31**	**11.0%**	**1.06 [0.38 , 2.93]**						
Total events:	8		5									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.10 (P = 0.92)												
21.1.4 Etidronate 400 mg/day versus HRT												
Wimalawansa 1998 (2)	3	17	2	18	3.6%	1.59 [0.30 , 8.37]		+	?	−	+	+
Subtotal (95% CI)		**17**		**18**	**3.6%**	**1.59 [0.30 , 8.37]**						
Total events:	3		2									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.55 (P = 0.59)												
21.1.5 Etidronate 400 mg/day versus etidronate 400 mg/day plus HRT												
Wimalawansa 1998 (2)	3	17	1	19	1.7%	3.35 [0.38 , 29.26]		+	?	−	+	+
Subtotal (95% CI)		**17**		**19**	**1.7%**	**3.35 [0.38 , 29.26]**						
Total events:	3		1									
Heterogeneity: Not applicable												
Test for overall effect: Z = 1.09 (P = 0.27)												
21.1.6 Etidronate 200 mg/day versus alendronate 5 mg/day												
Iwamoto 2005	0	25	0	25		Not estimable		−	−	−	+	−
Subtotal (95% CI)		**25**		**25**		**Not estimable**						
Total events:	0		0									
Heterogeneity: Not applicable												
Test for overall effect: Not applicable												
21.1.7 Etidronate 200 mg/day versus risedronate 2.5 mg/day												
Fukunaga 2002	2	106	0	101	0.9%	4.77 [0.23 , 98.08]		?	?	+	+	+
Subtotal (95% CI)		**106**		**101**	**0.9%**	**4.77 [0.23 , 98.08]**						
Total events:	2		0									
Heterogeneity: Not applicable												
Test for overall effect: Z = 1.01 (P = 0.31)												
21.1.8 Etidronate 200 mg/day versus alfacalcidol 1 µg/day												
Ishida 2004	8	66	11	66	20.1%	0.73 [0.31 , 1.69]		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**	**20.1%**	**0.73 [0.31 , 1.69]**						
Total events:	8		11									
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.74 (P = 0.46)												
21.1.9 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV												
Ishida 2004	8	66	8	66	14.6%	1.00 [0.40 , 2.51]		+	?	−	?	−
Subtotal (95% CI)		**66**		**66**	**14.6%**	**1.00 [0.40 , 2.51]**						

Analysis 21.1. (Continued)

Ishida 2004	8	66	8	66	14.6%	1.00 [0.40 , 2.51]
Subtotal (95% CI)		**66**		**66**	**14.6%**	**1.00 [0.40 , 2.51]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
21.1.10 Etidronate 200 mg/day versus HRT						
Ishida 2004 (3)	8	66	7	66	12.8%	1.14 [0.44 , 2.97]
Subtotal (95% CI)		**66**		**66**	**12.8%**	**1.14 [0.44 , 2.97]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
21.1.11 Etidronate 200 mg/day versus menatetrenone 45 mg/day						
Ishida 2004	8	66	9	66	16.5%	0.89 [0.37 , 2.16]
Iwamoto 2001	2	25	2	23	3.8%	0.92 [0.14 , 6.01]
Subtotal (95% CI)		**91**		**89**	**20.3%**	**0.89 [0.40 , 2.00]**
Total events:	10		11			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
21.1.12 Etidronate 200 mg/day versus etidronate 200 mg/day plus alfacalcidol 1 µg/day						
Iwamoto 2003b	1	20	1	20	1.8%	1.00 [0.07 , 14.90]
Subtotal (95% CI)		**20**		**20**	**1.8%**	**1.00 [0.07 , 14.90]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
21.1.13 Etidronate 400 mg/day plus HRT versus placebo						
Wimalawansa 1998 (2)	1	19	5	18	9.4%	0.19 [0.02 , 1.47]
Subtotal (95% CI)		**19**		**18**	**9.4%**	**0.19 [0.02 , 1.47]**
Total events:	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
21.1.14 Etidronate 400 mg/day plus HRT versus HRT						
Wimalawansa 1998 (2)	1	19	2	18	3.8%	0.47 [0.05 , 4.78]
Subtotal (95% CI)		**19**		**18**	**3.8%**	**0.47 [0.05 , 4.78]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**621**		**583**	**100.0%**	**0.95 [0.66 , 1.35]**
Total events:	53		53			
Heterogeneity: Chi² = 6.10, df = 11 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 6.09, df = 10 (P = 0.81), I² = 0%						



Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(2) HRT: [Premarin 0.625 mg/day + norgestrel 150 µg/day] for 12 days per month
(3) HRT: conjugated estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

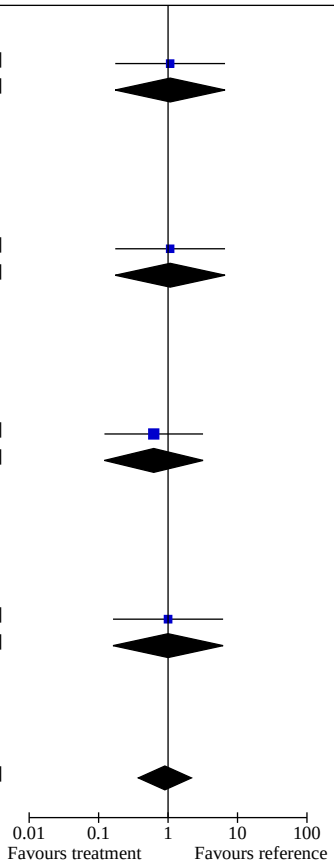
Comparison 22. Withdrawals due to adverse events

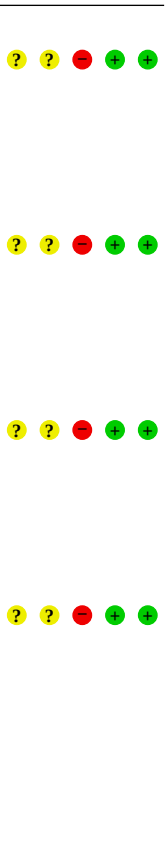
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Treatment versus reference, primary	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.37, 2.17]
22.1.1 Etidronate 400 mg/day versus HRT	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.17, 6.61]
22.1.2 Etidronate 400 mg/day versus etidronate 400 mg/day plus HRT	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.17, 6.61]
22.1.3 Etidronate 400 mg/day plus HRT versus placebo	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.12, 3.19]
22.1.4 Etidronate 400 mg/day plus HRT versus HRT	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.16, 6.20]
22.2 Treatment versus reference, secondary	10	1626	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.44, 0.97]
22.2.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.2.2 Etidronate 400 mg/day versus alendronate 10 mg/day	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.79]
22.2.3 Etidronate 400 mg/day versus intermittent/cyclic alendronate 10 mg/day	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.27]
22.2.4 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.2.5 Etidronate 400 mg/day versus calcitriol 0.5 µg/day	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.48]
22.2.6 Etidronate 400 mg/day versus fluoride 50 mg/day	1	118	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.67]
22.2.7 Etidronate 400 mg/day versus HRT	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.25, 4.54]
22.2.8 Etidronate 400 mg/day versus etidronate 400 mg/day + calcitriol 0.5 µg/day	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.40, 4.49]
22.2.9 Etidronate 400 mg/day versus etidronate 400 mg/day + HRT	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.22, 3.22]
22.2.10 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.2.11 Etidronate 200 mg/day versus risedronate 2.5 mg/day	1	235	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.33, 2.36]
22.2.12 Etidronate 200 mg/day versus alfacalcidol 1 µg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2.13 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]
22.2.14 Etidronate 200 mg/day versus HRT	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.12]
22.2.15 Etidronate 200 mg/day versus menatetrenone 45 mg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.33]
22.2.16 Etidronate 200 mg/day versus etidronate 200 mg/day + alfacalcidol 1 µg/day	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.2.17 Etidronate 400 mg/day + calcitriol 0.5 µg/day versus calcitriol 0.5 µg/day	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.2.18 Etidronate 400 mg/day + calcitriol 0.5 µg/day versus calcitonin 100 IU/2 days, IN + calcitriol 0.25 µg/day	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.2.19 Etidronate 400 mg/day + HRT versus placebo	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.33, 4.88]
22.2.20 Etidronate 400 mg/day + HRT versus HRT	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.33, 4.88]

Analysis 22.1. Comparison 22: Withdrawals due to adverse events, Outcome 1: Treatment versus reference, primary

Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI
22.1.1 Etidronate 400 mg/day versus HRT						
Wimalawansa 1995 (1)	2	14	2	15	21.5%	1.07 [0.17 , 6.61]
Subtotal (95% CI)		**14**		**15**	**21.5%**	**1.07 [0.17 , 6.61]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
22.1.2 Etidronate 400 mg/day versus etidronate 400 mg/day plus HRT						
Wimalawansa 1995 (1)	2	14	2	15	21.5%	1.07 [0.17 , 6.61]
Subtotal (95% CI)		**14**		**15**	**21.5%**	**1.07 [0.17 , 6.61]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
22.1.3 Etidronate 400 mg/day plus HRT versus placebo						
Wimalawansa 1995 (1)	2	15	3	14	34.6%	0.62 [0.12 , 3.19]
Subtotal (95% CI)		**15**		**14**	**34.6%**	**0.62 [0.12 , 3.19]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
22.1.4 Etidronate 400 mg/day plus HRT versus HRT						
Wimalawansa 1995 (1)	2	15	2	15	22.3%	1.00 [0.16 , 6.20]
Subtotal (95% CI)		**15**		**15**	**22.3%**	**1.00 [0.16 , 6.20]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**58**		**59**	**100.0%**	**0.90 [0.37 , 2.17]**
Total events:	8		9			
Heterogeneity: Chi² = 0.28, df = 3 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 0.28, df = 3 (P = 0.96), I² = 0%						





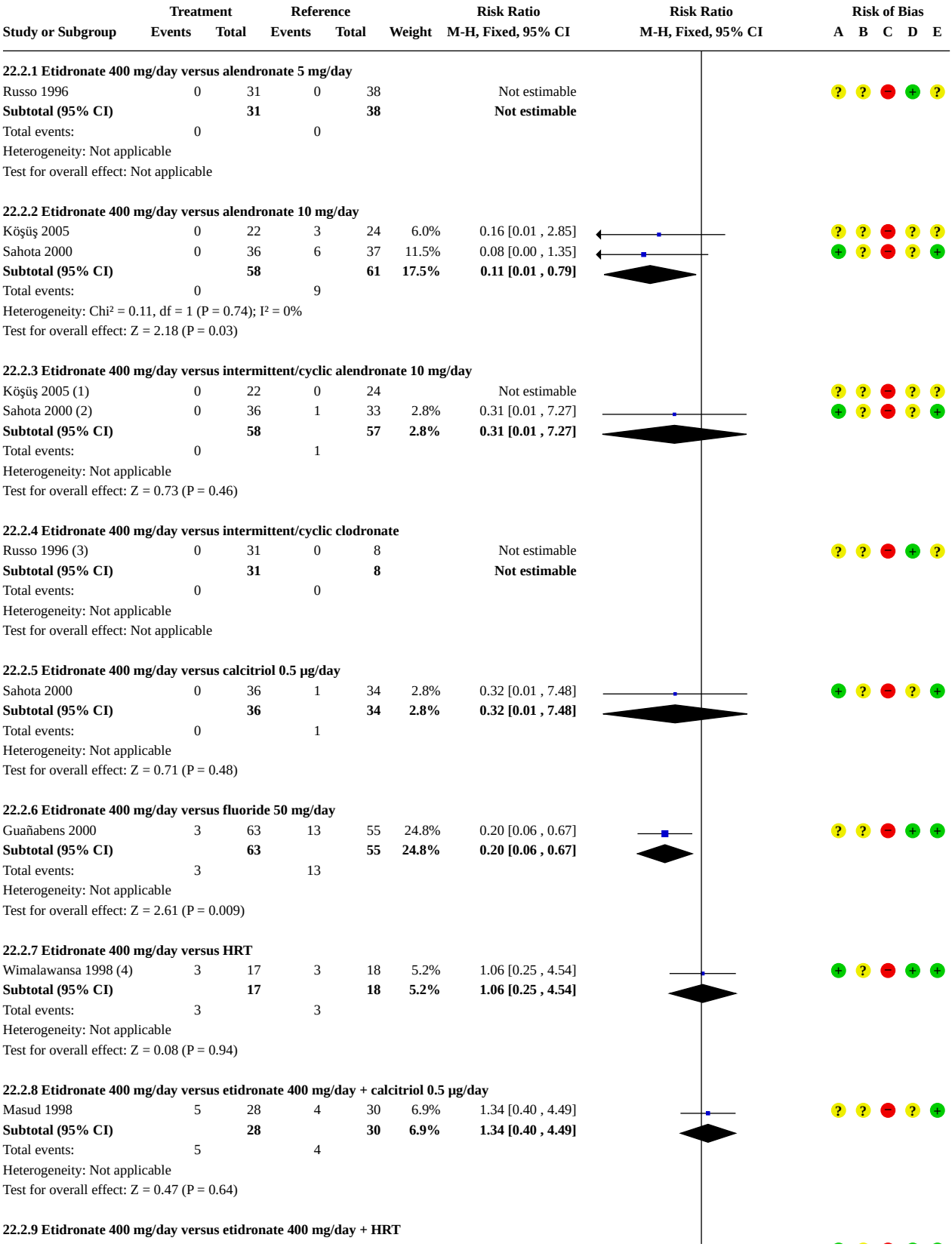
Footnotes

(1) HRT: [17B-E2 2.5 g/day (percutaneous Oestrogel)] + 12-day micronized progesterone 200 mg/day each month + 1 g/day elemental calcium supplements

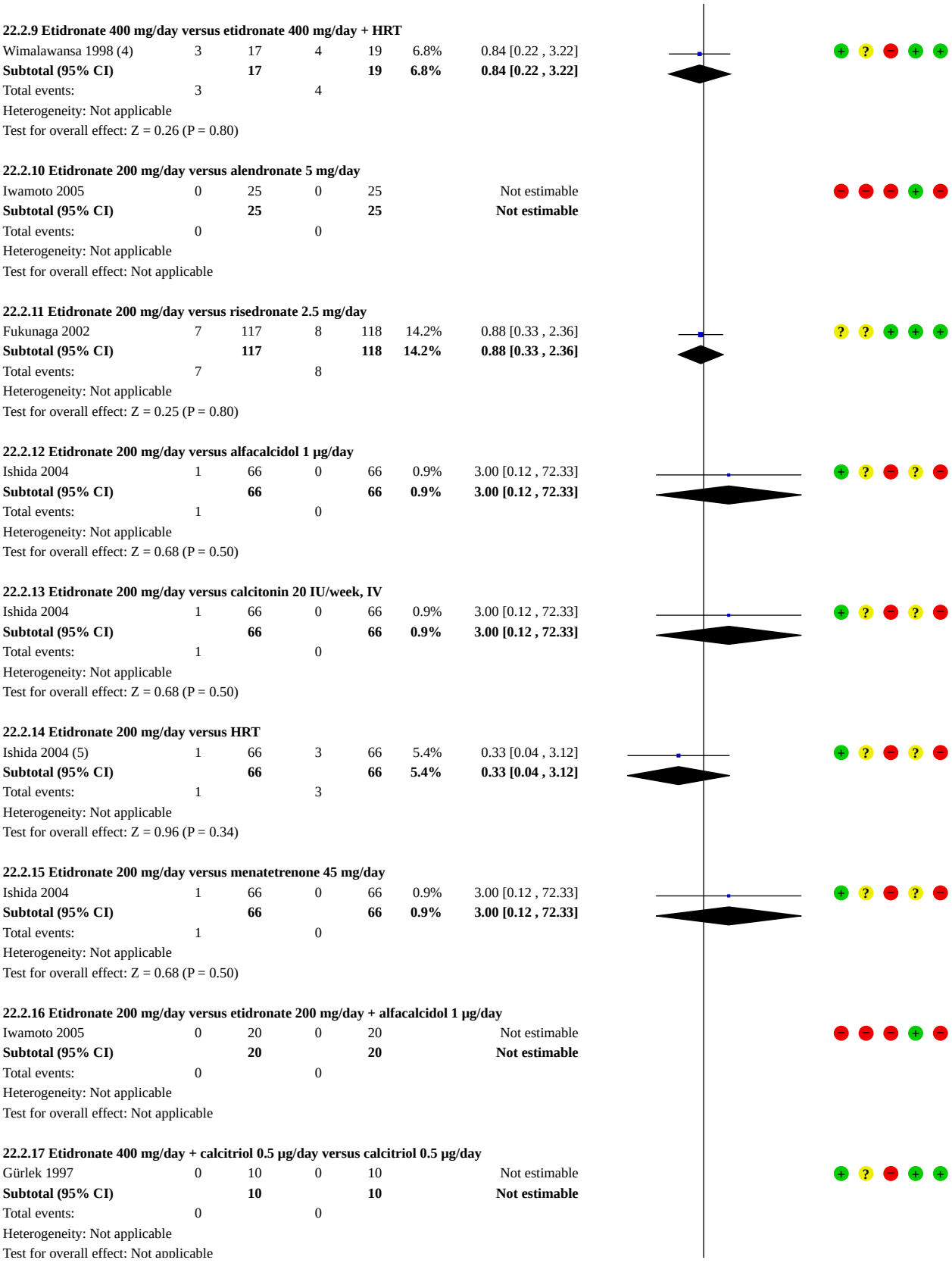
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 22.2. Comparison 22: Withdrawals due to adverse events, Outcome 2: Treatment versus reference, secondary



Analysis 22.2. (Continued)



22.2.9 Etidronate 400 mg/day versus etidronate 400 mg/day + HRT

Wimalawansa 1998 (4)	3	17	4	19	6.8%	0.84 [0.22 , 3.22]
Subtotal (95% CI)		**17**		**19**	**6.8%**	**0.84 [0.22 , 3.22]**
Total events:	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)

22.2.10 Etidronate 200 mg/day versus alendronate 5 mg/day

Iwamoto 2005	0	25	0	25		Not estimable
Subtotal (95% CI)		**25**		**25**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

22.2.11 Etidronate 200 mg/day versus risedronate 2.5 mg/day

Fukunaga 2002	7	117	8	118	14.2%	0.88 [0.33 , 2.36]
Subtotal (95% CI)		**117**		**118**	**14.2%**	**0.88 [0.33 , 2.36]**
Total events:	7		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

22.2.12 Etidronate 200 mg/day versus alfacalcidol 1 µg/day

Ishida 2004	1	66	0	66	0.9%	3.00 [0.12 , 72.33]
Subtotal (95% CI)		**66**		**66**	**0.9%**	**3.00 [0.12 , 72.33]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

22.2.13 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV

Ishida 2004	1	66	0	66	0.9%	3.00 [0.12 , 72.33]
Subtotal (95% CI)		**66**		**66**	**0.9%**	**3.00 [0.12 , 72.33]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

22.2.14 Etidronate 200 mg/day versus HRT

Ishida 2004 (5)	1	66	3	66	5.4%	0.33 [0.04 , 3.12]
Subtotal (95% CI)		**66**		**66**	**5.4%**	**0.33 [0.04 , 3.12]**
Total events:	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

22.2.15 Etidronate 200 mg/day versus menatetrenone 45 mg/day

Ishida 2004	1	66	0	66	0.9%	3.00 [0.12 , 72.33]
Subtotal (95% CI)		**66**		**66**	**0.9%**	**3.00 [0.12 , 72.33]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

22.2.16 Etidronate 200 mg/day versus etidronate 200 mg/day + alfacalcidol 1 µg/day

Iwamoto 2005	0	20	0	20		Not estimable
Subtotal (95% CI)		**20**		**20**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

22.2.17 Etidronate 400 mg/day + calcitriol 0.5 µg/day versus calcitriol 0.5 µg/day

Gürlek 1997	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Analysis 22.2. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Not applicable

22.2.18 Etidronate 400 mg/day + calcitriol 0.5 µg/day versus calcitonin 100 IU/2 days, IN + calcitriol 0.25 µg/day

Gürlek 1997	0	10	0	10		Not estimable
Subtotal (95% CI)		**10**		**10**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

22.2.19 Etidronate 400 mg/day + HRT versus placebo

Wimalawansa 1998 (4)	4	19	3	18	5.5%	1.26 [0.33 , 4.88]
Subtotal (95% CI)		**19**		**18**	**5.5%**	**1.26 [0.33 , 4.88]**
Total events:	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

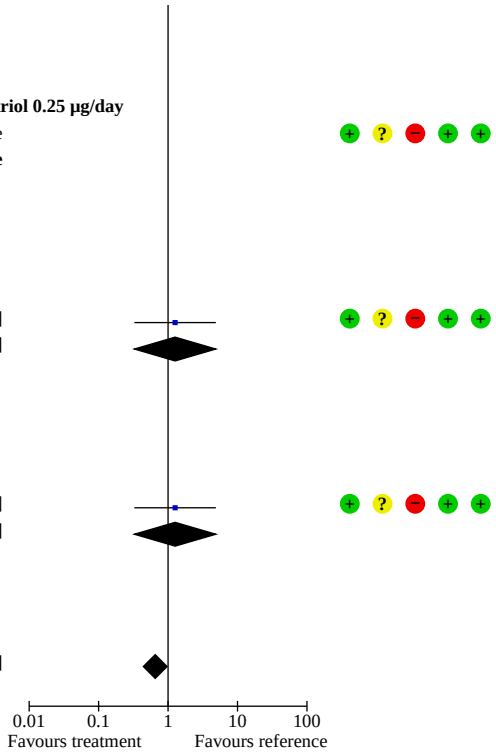
22.2.20 Etidronate 400 mg/day + HRT versus HRT

Wimalawansa 1998 (4)	4	19	3	18	5.5%	1.26 [0.33 , 4.88]
Subtotal (95% CI)		**19**		**18**	**5.5%**	**1.26 [0.33 , 4.88]**
Total events:	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

Total (95% CI)		**823**		**803**	**100.0%**	**0.65 [0.44 , 0.97]**
Total events:	33		52			

Heterogeneity: Chi² = 14.25, df = 14 (P = 0.43); I² = 2%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Chi² = 13.88, df = 13 (P = 0.38), I² = 6.3%



Footnotes
(1) intermittent/cyclic Alendronate: Alendronate 10 mg/day for 14 days, followed by 76 days of calcium tablets for 1 year.
(2) intermittent/cyclic Alendronate: Alendronate 10 mg once daily in 3-monthly cycles on/off for 60 weeks.
(3) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(4) HRT: [Premarin 0.625 mg/day + norgestrel 150 µg/day] for 12 days per month
(5) HRT: conjugated estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 23. Serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Treatment versus reference, secondary	3	195	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
23.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
23.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1.3 Etidronate 400 mg/day versus ADFR	1	37	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
23.1.4 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 23.1. Comparison 23: Serious adverse events, Outcome 1: Treatment versus reference, secondary

Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI
23.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day						
Russo 1996	0	31	0	38		Not estimable
Subtotal (95% CI)		**31**		**38**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
23.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate						
Russo 1996 (1)	0	31	0	8		Not estimable
Subtotal (95% CI)		**31**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
23.1.3 Etidronate 400 mg/day versus ADFR						
Steiniche 1991 (2)	0	19	0	18		Not estimable
Subtotal (95% CI)		**19**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
23.1.4 Etidronate 200 mg/day versus alendronate 5 mg/day						
Iwamoto 2005	0	25	0	25		Not estimable
Subtotal (95% CI)		**25**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**106**		**89**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(2) ADFR: four repeated cycle of (7 day triiodothyronine 100 µg/day → 2-week etidronate 400 mg/day → 12-week drug-free).

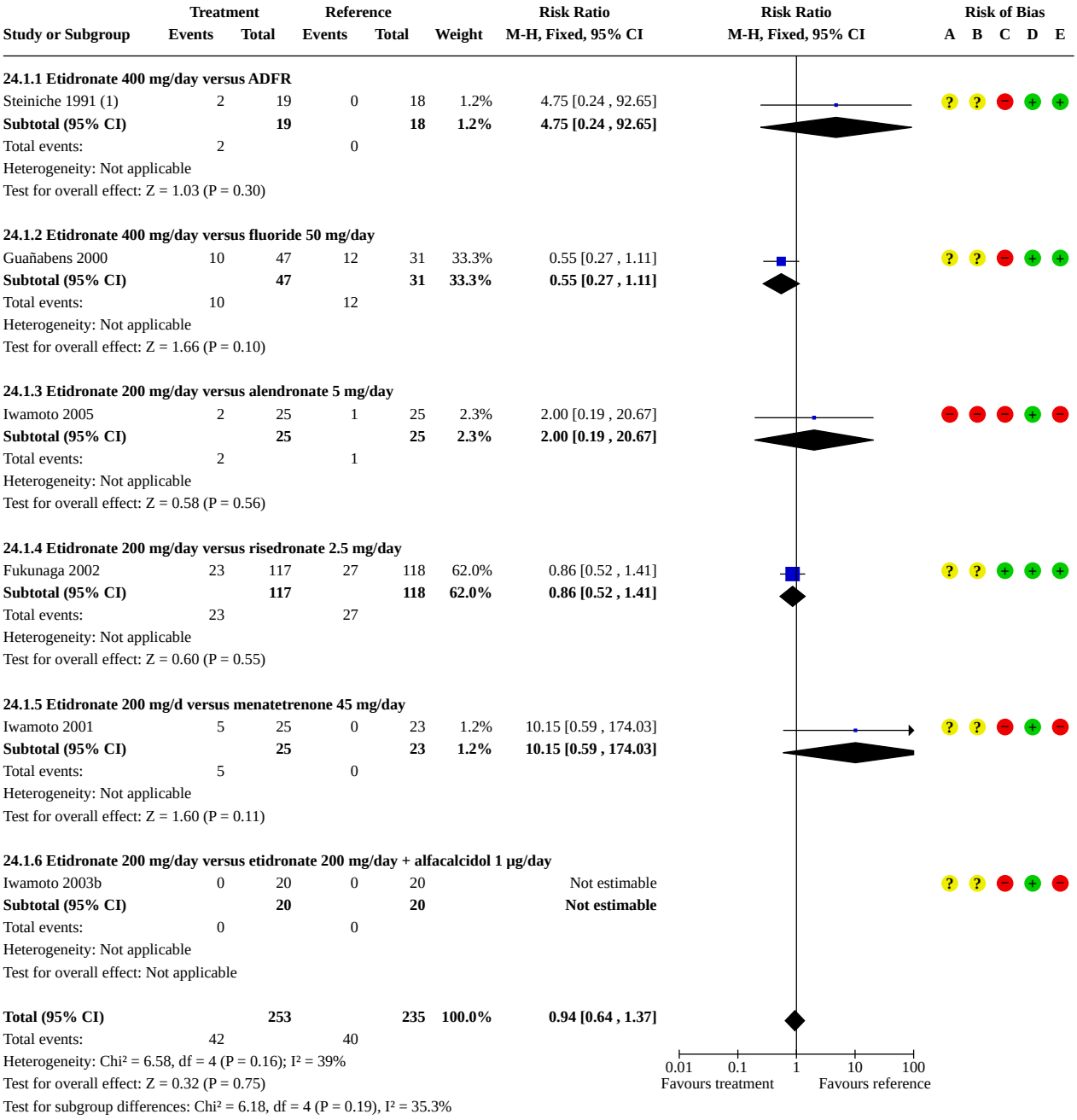
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 24. Gastrointestinal adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Treatment versus reference, secondary	6	488	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.64, 1.37]
24.1.1 Etidronate 400 mg/day versus ADFR	1	37	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [0.24, 92.65]
24.1.2 Etidronate 400 mg/day versus fluoride 50 mg/day	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.11]
24.1.3 Etidronate 200 mg/day versus alendronate 5 mg/day	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.19, 20.67]
24.1.4 Etidronate 200 mg/day versus risedronate 2.5 mg/day	1	235	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.52, 1.41]
24.1.5 Etidronate 200 mg/d versus menatetrenone 45 mg/day	1	48	Risk Ratio (M-H, Fixed, 95% CI)	10.15 [0.59, 174.03]
24.1.6 Etidronate 200 mg/day versus etidronate 200 mg/day + alfacalcidol 1 µg/day	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 24.1. Comparison 24: Gastrointestinal adverse events, Outcome 1: Treatment versus reference, secondary



Footnotes

(1) ADFR: four repeated cycle of (7 day triiodothyronine 100 µg/day → 2-week etidronate 400 mg/day→ 12-week drug-free).

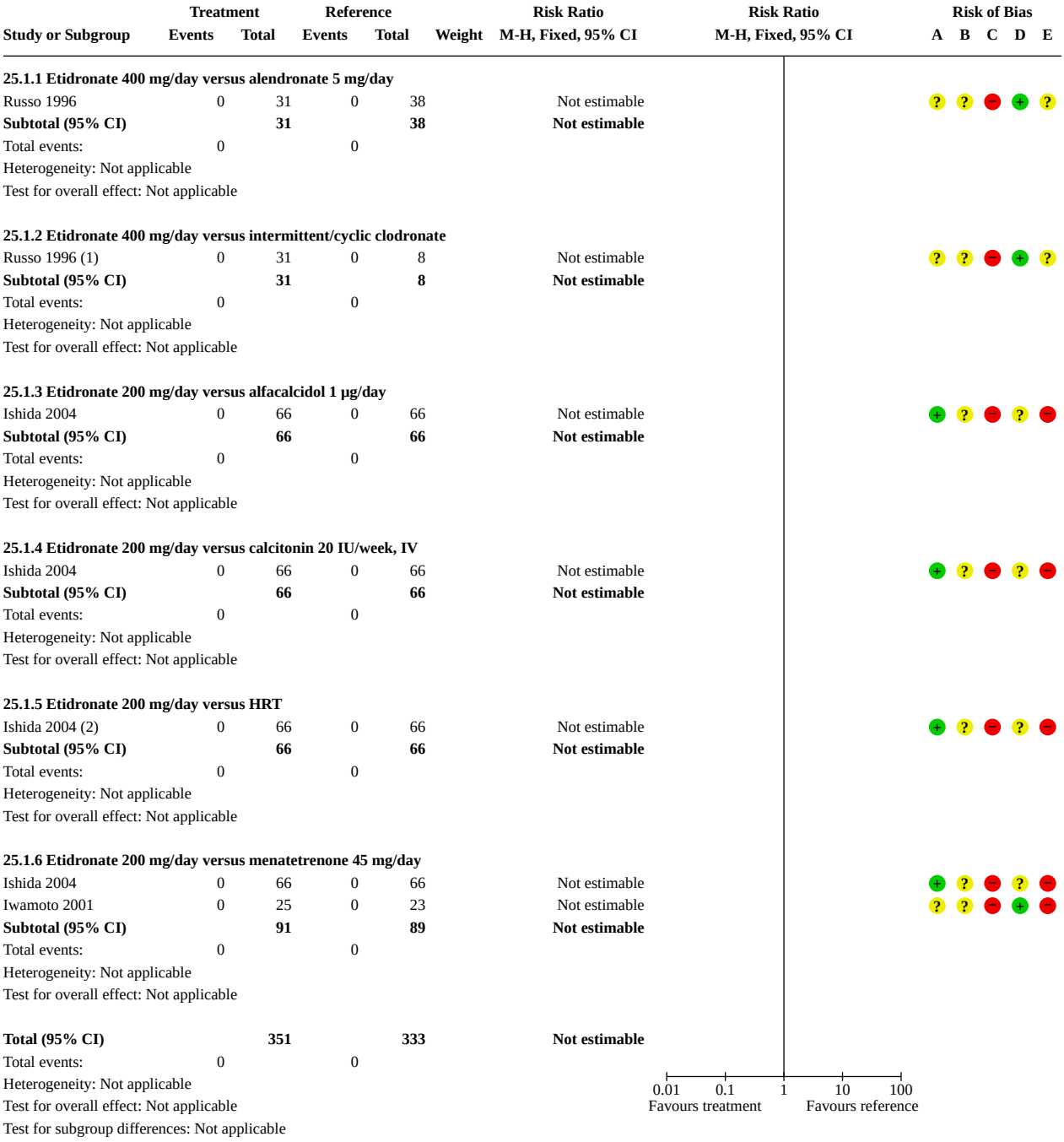
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Comparison 25. Atypical femoral fracture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Treatment versus reference, secondary	3	684	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
25.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
25.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
25.1.3 Etidronate 200 mg/day versus alfacalcidol 1 µg/day	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
25.1.4 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
25.1.5 Etidronate 200 mg/day versus HRT	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
25.1.6 Etidronate 200 mg/day versus menatetrenone 45 mg/day	2	180	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 25.1. Comparison 25: Atypical femoral fracture, Outcome 1: Treatment versus reference, secondary



Study or Subgroup	Treatment Events	Treatment Total	Reference Events	Reference Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E
25.1.1 Etidronate 400 mg/day versus alendronate 5 mg/day											
Russo 1996	0	31	0	38		Not estimable	?	?	−	+	?
Subtotal (95% CI)		**31**		**38**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
25.1.2 Etidronate 400 mg/day versus intermittent/cyclic clodronate											
Russo 1996 (1)	0	31	0	8		Not estimable	?	?	−	+	?
Subtotal (95% CI)		**31**		**8**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
25.1.3 Etidronate 200 mg/day versus alfacalcidol 1 µg/day											
Ishida 2004	0	66	0	66		Not estimable	+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
25.1.4 Etidronate 200 mg/day versus calcitonin 20 IU/week, IV											
Ishida 2004	0	66	0	66		Not estimable	+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
25.1.5 Etidronate 200 mg/day versus HRT											
Ishida 2004 (2)	0	66	0	66		Not estimable	+	?	−	?	−
Subtotal (95% CI)		**66**		**66**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
25.1.6 Etidronate 200 mg/day versus menatetrenone 45 mg/day											
Ishida 2004	0	66	0	66		Not estimable	+	?	−	?	−
Iwamoto 2001	0	25	0	23		Not estimable	?	?	−	+	−
Subtotal (95% CI)		**91**		**89**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
Total (95% CI)		**351**		**333**		**Not estimable**					
Total events:	0		0								
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
Test for subgroup differences: Not applicable											

Footnotes

(1) Intermittent/cyclic clodronate: repeated cycles of (20-day clodronate 100 mg/day, IM → 10-day break → 2-month oral clodronate 400 mg/day → 1-month break).
(2) HRT: conjugated estrogen 0.625 mg/day plus medroxyprogesterone 2.5 mg/day

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 25.1. (Continued)

(D) Selective reporting (reporting bias)
(E) Other bias

ADDITIONAL TABLES

Table 1. Classification of primary and secondary prevention studies

CLASSIFICATION:	CLASSIFICATION CRITERIA ASSESSED:						TOTAL STUDIES CLASSIFIED (N = 30)
	Using study eligibility criteria				Using participant baseline characteristics		
	Diagnosis*	History of VF	History of VF or BMD T-score	BMD T-score	Mean BMD T-score	Age	
Number of studies included in quantitative analysis (K = 26)							
Primary	1	6	NA	4	2	8	9
Secondary	16	8	4	3	3	0	17
Number of included studies excluded from quantitative analysis (k = 4)							
Primary	0	0	NA	0	0	1	1
Secondary	3	2	1	0	0	0	3

BMD: bone mineral density; NA= not available; VF: vertebral fractures

*Diagnosis of osteopenia for primary prevention trials, and osteoporosis for secondary prevention trials, following the diagnostic criteria of WHO 1994 [WHO 1994].

Table 2. Relative risk of major outcomes after etidronate versus placebo

Major outcomes	Primary / secondary prevention	No. of studies	No. of participants (etidronate / placebo)	Relative risk (95% CI)	Association P value	Heterogeneity P value
Etidronate 400 mg/day versus placebo						
Clinical vertebral fractures	Primary	2	81 / 82	3.03(0.32 to 28.44)	0.33	0.99
	Secondary	0	0 / 0	NA	NA	NA
Non-vertebral fractures	Primary	2	81 / 82	0.56 (0.20 to 1.61)	0.28	0.81
	Secondary	4*	301 / 297	1.06 (0.71 to 1.58)	0.77	0.83
Hip fractures	Primary	2	94 / 95	NE	NA	NA
	Secondary	2	144 / 139	0.93 (0.17 to 5.19)	0.94	0.35
Wrist fractures	Primary	0	0 / 0	NA	NA	NA
	Secondary	2	72 / 68	0.90 (0.13 to 6.04)	0.91	NA
Withdrawals due to adverse events	Primary	8	298 / 299	1.41 (0.81 to 2.47)	0.23	0.12
	Secondary	4*	312 / 312	1.09 (0.54 to 2.18)	0.81	0.98
Serious adverse events	Primary	5	246 / 251	0.90 (0.52 to 1.54)	0.69	0.52
	Secondary	1	50 / 50	NE	NA	NA
Etidronate 200 mg/day versus placebo						
Hip fractures	Primary	0	0 / 0	NA	NA	NA
	Secondary	2	91 / 90	0.33 (0.01 to 8.04)	0.50	NA
Wrist fractures	Primary	0	0 / 0	NA	NA	NA
	Secondary	2	91 / 90	NE	NA	NA
Withdrawals due to adverse events	Primary	0	0 / 0	NA	NA	NA
	Secondary	1	66 / 66	3.00 (0.12 to 72.33)	0.50	NA
Serious adverse events	Primary	0	0 / 0	NA	NA	NA
	Secondary	1	20 / 20	NE	NA	NA

CI: confidence interval; **NA:** not available; **NE:** not estimable

*Data from Watts 1990 was extracted as two pair-wise comparisons of etidronate versus placebo. The arm of [Phosphate 2 g/day for day 1-3, followed by etidronate 400 mg/day for day 4-17 and calcium 500 mg/day for day 18-91] and [Phosphate 2 g/day for day 1-3, followed by placebo for day 4-17 and calcium 500 mg/day for day 18-91] were regarded as etidronate 400 mg/day compared with placebo.

Table 3. Relative risk of minor outcomes after etidronate versus placebo

Safety outcomes	Primary / secondary prevention	No. of studies	No. of participants (etidronate / placebo)	Relative risk (95% CI)	Association P value	Heterogeneity P value
Etidronate 400 mg/day versus placebo						
Radiographic vertebral fractures	Primary	2	115 / 117	0.14 (0.01 to 2.68)	0.19	NA
	Secondary	3*	251 / 236	***0.46 (0.26 to 0.82)***	0.02	0.86
Gastrointestinal adverse events	Primary	1	74 / 76	0.54 (0.26 to 1.14)	0.11	NA
	Secondary	0	0 / 0	NA	NA	NA
Atypical femoral fracture	Primary	2	94 / 95	NE	NA	NA
	Secondary	1	50 / 50	NE	NA	NA
Etidronate 200 mg/day versus placebo						
Radiographic vertebral fractures	Primary	0	0 / 0	NA	NA	NA
	Secondary	3	111 / 110	***0.32 (0.17 to 0.60)***	0.0004	0.28
Gastrointestinal adverse events	Primary	0	0 / 0	NA	NA	NA
	Secondary	1	25 / 24	2.40 (0.51 to 11.21)	0.27	NA
Atypical femoral fracture	Primary	0	0 / 0	NA	NA	NA
	Secondary	2	91 / 90	NE	NA	NA

CI: confidence interval; **NA:** not available; **NE:** not estimable.

Table 4. Five-year risks of fracture reduced after etidronate

Fracture site RR (95% CI)	FRACTURE Index*	Risk*, % (untreated)	Risk, % (treated)	RRR, %	ARR, %	NNT
Etidronate 400 mg/day for secondary prevention						
Radiographic vertebral ***0.46 (0.26 to 0.82)***	1-2	1.2	0.6	0.54	0.6	154
	3-4	2.5	1.2	0.54	1.4	74
	5	5.3	2.4	0.54	2.9	35

Table 4. Five-year risks of fracture reduced after etidronate *(Continued)*

	6-7	7.1	3.3	0.54	3.8	26
	8-13	11.2	5.2	0.54	6.0	17
Etidronate 200 mg/day for secondary prevention						
Radiographic vertebral	1-2	1.2	0.4	0.68	0.8	123
0.32 (0.17 to 0.60)	3-4	2.5	0.8	0.68	1.7	59
	5	5.3	1.7	0.68	3.6	28
	6-7	7.1	2.3	0.68	4.8	21
	8-13	11.2	3.6	0.68	7.6	13

ARR: absolute risk reduction; **CI:** confidence interval; **NNT:** number needed to treat; **RR:** relative risk; **RRR:** relative risk reduction
*Five-year risk of fractures by quintile of the FRACTURE Index (FI) score (Appendix 3; Black 2001).

Table 5. Five-year age-specific absolute risk reduction (number need to treat for an additional beneficial outcome) of first and subsequent fracture after etidronate

Age group (years)	Fracture	Etidronate 400 mg/day	Etidronate 200 mg/day
		Radiographic vertebral ***0.47 (0.25,0.90)***	**Radiographic vertebral** ***0.32 (0.17,0.60)***
50 to 54	**First**	0. 1% (926)	0. 1% (735)
	Subsequent	0.3% (370)	0.3% (294)
55 to 59	**First**	0.2% (463)	0.3% (368)
	Subsequent	2.2% (46)	2.7% (37)
60 to 64	**First**	0.5% (185)	0.7% (147)
	Subsequent	5.2% (19)	6.6% (15)
65 to 69	**First**	0.8% (123)	1.0% (98)
	Subsequent	7.7% (13)	9.7% (10)
70 to 74	**First**	1.0% (103)	1.2% (82)
	Subsequent	9.3% (11)	11.7% (9)
75 to 79	**First**	1.8% (56)	2.2% (45)
	Subsequent	13.1% (8)	16.5% (6)
80 to 84	**First**	1.2% (81)	1.6% (64)
	Subsequent	10.3% (10)	13.0% (8)

Table 5. Five-year age-specific absolute risk reduction (number need to treat for an additional beneficial outcome) of first and subsequent fracture after etidronate *(Continued)*

85 to 89	**First**	1.4% (74)	1.7% (59)
	Subsequent	11.3% (9)	14.2% (7)
90+	**First**	2.5% (39)	3.2% (31)
	Subsequent	15.1% (7)	19.0% (5)

Age-specific absolute risk reduction (ARR) = (1- relative risk after alendronate) *age-specific risk retrieved from Appendix 4 (Doherty 2001 [Doherty 2001]).
Number needed to treat (NNT) = 1/ARR.

Table 6. Relative risk of fracture after etidronate 400 mg/day: subgroup analyses

Fracture site	Primary/ secondary Prevention	Base case	Treatment years				Prior bisphosphonate experience
			Year 1	Year 2	Year 3	Year 4	Bisphosphonate-naïve
Clinical vertebral	Primary	2 / 163 3.03 (0.32, 28.44)	NA	2 / 163 3.03 (0.32, 28.44)	NA	NA	1 / 54 3.00 (0.13,70.53)
	Secondary	NA	NA	NA	NA	NA	NA
Non-vertebral	Primary	2 / 163 0.56 (0.20, 1.61)	NA	2 / 163 0.56 (0.20, 1.61)	NA	NA	1 / 54 0.67 (0.12,3.68)
	Secondary	4* / 598 1.07 (0.72, 1.58)	NA	1* / 423 1.21 (0.76, 1.92)	1 / 66 0.83 (0.28, 2.46)	2 / 135 0.67 (0.20, 2.28)	3* / 524 1.14 (0.75,1.73)
Hip	Primary	2 / 189 NE	NA	1 / 109 NE	1 / 80 NE	NA	NA
	Secondary	2 / 193 0.93 (0.17,5.19)	NA	1 / 209 2.97 (0.12, 72.12)	NA	1 / 100 0.50 (0.05, 5.34)	1 / 209 2.97 (0.12,72.12)
Wrist	Primary	NA	NA	NA	NA	NA	NA
	Secondary	2 / 140 0.90 (0.13,6.04)	NA	NA	1 / 66 NE	1 / 100 1.00 (0.14,7.39)	1 /66 NE
Radiographic vertebral	Primary	2 / 232 0.14 (0.01,2.68)	NA	2 / 232 0.14 (0.01,2.68)	1 / 80 0.14 (0.01,2.68)	NA	1 / 152 NE
	Secondary	3* / 487 ***0.46 (0.26,0.82)***	1 / 95 0.16 (0.02,1.25)	2* / 469 ***0.33 (0.17,0.67)***	1 / 82 ***0.29 (0.10,0.82)***	2 / 109 0.48 (0.21,1.09)	2* / 413 ***0.48 (0.24,0.96)***

Number of studies/number of participants, relative risk (95% confidence interval); **NA:** not available; **NE:** not estimable.

*Data from Watts 1990 was extracted as two pair-wise comparisons of Etidronate versus placebo. The arm of [Phosphate 2 g/day for day 1-3, followed by etidronate 400 mg/day for day 4-17 and calcium 500 mg/day for day 18-91] and [Phosphate 2 g/day for day 1-3, followed by placebo for day 4-17 and calcium 500 mg/day for day 18-91] were regarded as etidronate 400 mg/day compared with placebo.

Table 7. Relative risk of fractures after etidronate 200 mg/day for secondary prevention: base case, subgroup and sensitivity analyses

Fracture Site	Base case	Subgroup analyses			Sensitivity analyses with	
		Year 1	Year 2	Bisphosphonate -naïve	Baseline denominators	Studies taking fractures as efficacy outcomes
Hip	2 / 181 0.33 (0.01,8.04)	NA	2 / 181 0.33 (0.01,8.04)	1 / 49 NE	2 / 181 0.33 (0.01,8.04)	2 / 181 0.33 (0.01,8.04)
Wrist	2 / 181 NE	NA	2 / 181 NE	1 / 49 NE	2 / 181 NE	2 / 181 NE
Radiographic vertebral	3 / 221 ***0.32 (0.17,0.60)***	1 / 132 0.56 (0.20,1.57)	3 / 221 ***0.32 (0.17,0.60)***	1 / 49 0.32 (0.07,1.43)	3 / 221 ***0.32 (0.17,0.60)***	2 / 181 ***0.43 (0.22,0.85)***

Number of studies/number of participants, relative risk (95% confidence interval); **NA:** not available; **NE:** not estimable.

Table 8. Relative risk of fracture after etidronate 400 mg/day versus placebo: sensitivity analyses

Fracture site	Primary/ secondary prevention	Base case	Sensitivity analysis:			
			Using baseline denominators	Studies taking fractures as efficacy outcomes	Excluding primary/secondary studies using age criterion alone	Excluding studies applying ADFR regimen
Clinical vertebral	Primary	2 / 163 3.03 (0.32, 28.44)	2 / 163 3.03 (0.32, 28.44)	NA	1 / 54 3.00 (0.13, 70.53)	2 / 163 3.03 (0.32, 28.44)
	Secondary	NA	NA	NA	NA	NA
Non-vertebral	Primary	2 / 163 0.56 (0.20, 1.61)	2 / 163 0.56 (0.20, 1.61)	NA	1 / 54 0.67 (0.12, 3.68)	2 / 163 0.56 (0.20, 1.61)
	Secondary	4* / 598 1.07 (0.72, 1.58)	4* / 624 1.07 (0.72, 1.60)	4* / 624 1.07 (0.72, 1.60)	4* / 624 1.07 (0.72, 1.60)	3 / 310 1.13 (0.67, 1.88)
Hip	Primary	2 / 189 NE	2 / 189 NE	1 / 80 NE	NA	2 / 189 NE
	Secondary	2 / 293 0.93 (0.17,5.19)	2 / 309 1.00 (0.18,5.66)	2 / 309 1.00 (0.18,5.66)	2 / 309 1.00 (0.18,5.66)	1 / 209 2.97 (0.12,72.12)

Table 8. Relative risk of fracture after etidronate 400 mg/day versus placebo: sensitivity analyses *(Continued)*

Wrist	Primary	NA	NA	NA	NA	NA
	Secondary	2 / 140	2 / 166	2 / 166	2 / 166	1 / 66
		0.90 (0.13,6.04)	1.00 (0.15,6.82)	1.00 (0.15,6.82)	1.00 (0.15,6.82)	NE
Radiographic vertebral	Primary	2 / 232	2 / 232	2 / 232	1 / 152	2 / 232
		0.14 (0.01,2.68)	0.14 (0.01,2.68)	0.14 (0.01,2.68)	NE	0.14 (0.01,2.68)
	Secondary	3* / 487	3* / 558	3* / 487	3* / 487	2 / 224
		0.46 (0.26,0.82)	***0.49 (0.27,0.87)***	***0.46 (0.26,0.82)***	***0.46 (0.26,0.82)***	0.52 (0.23,1.16)

Number of studies/number of participants, relative risk (95% confidence interval); **ADFR:** repeated cycle of activation, depression, free, repeat; **NA:** not available; **NE:** not estimable.
*Data from Watts 1990 was extracted as two pair-wise comparisons of Etidronate versus placebo. The arm of [Phosphate 2 g/day for day 1-3, followed by etidronate 400 mg/day for day 4-17 and calcium 500 mg/day for day 18-91] and [Phosphate 2 g/day for day 1-3, followed by placebo for day 4-17 and calcium 500 mg/day for day 18-91] were regarded as etidronate 400 mg/day compared with placebo.

APPENDICES

Appendix 1. Search strategies for etidronate updated review: 2012, 2017, 2019, 2021, and 2023

1-1 Search results and strategies in June 2012

Search date	Database, and coverage	Number of references retrieved	Number of references after de-duplication
28 June 2012	**Ovid MEDLINE(R) 1946- 2012**	571	415
28 June 2012	**Embase Classic+Embase 1947-2012**	172	170
28 June 2012	**Cochrane Library Issue**		
	- Cochrane Reviews	3	0
	- DARE	5	0
	- Economic Evaluations	9	0
	- Technology Assessments	4	0
	- Methods Studies	4	2
	- Trials	179	16
Total		**947**	**603**

MEDLINE

1. Osteoporosis/

2. osteop$.tw.

3. bone density/

4. (bone adj2 densit$).tw.

5. bmd.tw.

6. exp "Bone and Bones"/

7. bone loss$.tw.

8. or/1-7

9. exp Menopause/

10. menopaus$.tw.

11. postmenopaus$.tw.

12. or/9-11

13. 8 and 12

14. Osteoporosis, Postmenopausal/

15. 13 or 14

16. Etidronic Acid/

17. etidronate.tw.

18. Anfozan.tw.

19. Biotredine.tw.

20. Bonemass.tw.

21. Detidron.tw.

22. Didrocal.tw.

23. (didrokit or (didro adj kit)).tw..

24. Didronat$.tw.

25. Didronel.tw.

26. Difosfen.tw.

27. Diphos.tw.

28. Dralen.tw.

29. Dronate-OS.tw.

30. ehdp.tw.

31. ethanehydroxydiphosphonate.tw.

32. Emoform Total.tw.

33. Eopon.tw.

34. Etidrate.tw.

35. Etidrel.tw.

36. Etidron.tw.

37. Etiplus.tw.

38. Feminoflex.tw.

39. Gen-Eti-Cal.tw.

40. Maxibral.tw.

41. Oflocin.tw.

42. Osfo.tw.

43. Ostedron.tw.

44. Osteodidronel.tw.

45. Osteodrug.tw.

46. Osteoto$.tw.

47. Osteum.tw.

48. Ostogene.tw.

49. Ostopor.tw.

50. Somaflex.tw.

51. Squam.tw.

52. Sterodome.tw.

53. Sviroxit.tw.

54. Tilferan.tw.

55. Tiloetca Combi.tw.

56. Xidifon.tw.

57. xidiphon$.tw.

58. or/16-57

59. 15 and 58

60. randomized controlled trial.pt.

61. controlled clinical trial.pt.

62. randomized.ab.

63. placebo.ab.

64. drug therapy.fs.

65. randomly.ab.

66. trial.ab.

67. groups.ab.

68. or/60-67

69. (animals not (humans and animals)).sh.

70. 68 not 69

71. 59 and 70

EMBASE

1. Osteoporosis/

2. osteop$.tw.

3. bone density/

4. (bone adj2 densit$).tw.

5. bmd.tw.

6. bone loss$.tw.

7. or/1-6

8. menopause/

9. menopaus$.tw.

10. postmenopaus$.tw.

11. or/8-10

12. 7 and 11

13. postmenopause osteoporosis/

14. 12 or 13

15. etidronic acid/

16. etidronate.tw.

17. Anfozan.tw.

18. Biotredine.tw.

19. Bonemass.tw.

20. Detidron.tw.

21. Didrocal.tw.

22. (didrokit or (didro adj kit)).tw.

23. Didronat$.tw.

24. Didronel.tw.

25. Difosfen.tw.

26. Diphos.tw.

27. Dralen.tw.

28. Dronate-OS.tw.

29. ehdp.tw.

30. ethanehydroxydiphosphonate.tw.

31. Emoform Total.tw.

32. Eopon.tw.

33. Etidrate.tw.

34. Etidrel.tw.

35. Etidron.tw.

36. Etiplus.tw.

37. Feminoflex.tw.

38. Gen-Eti-Cal.tw.

39. Maxibral.tw.

40. Oflocin.tw.

41. Osfo.tw.

42. Ostedron.tw.

43. Osteodidronel.tw.

44. Osteodrug.tw.

45. Osteoto$.tw.

46. Osteum.tw.

47. Ostogene.tw.

48. Ostopor.tw.

49. Somaflex.tw.

50. Squam.tw.

51. Sterodome.tw.

52. Sviroxit.tw.

53. Tilferan.tw.

54. Tiloetca Combi.tw.

55. Xidifon.tw.

56. xidiphon$.tw.

57. or/15-56

58. 14 and 57

59. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

60. RETRACTED ARTICLE/

61. 59 or 60

62. (animal$ not human$).sh,hw.

63. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/

64. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/

65. 61 not (62 or 63 or 64)

66. 58 and 65

The Cochrane Library

#1 MeSH descriptor Osteoporosis, this term only

#2 osteop*:ti,ab

#3 MeSH descriptor Bone Density, this term only

#4 (bone near/2 densit*):ti,ab

#5 bmd:ti,ab

#6 MeSH descriptor Bone and Bones explode all trees

#7 bone next loss*:ti,ab

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 MeSH descriptor Menopause explode all trees

#10 menopaus*:ti,ab

#11 postmenopaus*:ti,ab

#12 (#9 OR #10 OR #11)

#13 (#8 AND #12)

#14 MeSH descriptor Osteoporosis, Postmenopausal, this term only

#15 (#13 OR #14)

#16 MeSH descriptor Etidronic Acid, this term only

#17 etidronate:ti,ab

#18 Anfozan:ti,ab

#19 Biotredine:ti,ab

#20 Bonemass:ti,ab

#21 Detidron:ti,ab

#22 Didrocal:ti,ab

#23 didrokit:ti,ab or "didro-kit":ti,ab or didro next kit:ti,ab

#24 Didronat*:ti,ab

#25 Didronel:ti,ab

#26 Difosfen:ti,ab

#27 Diphos:ti,ab

#28 Dralen:ti,ab

#29 Dronate-OS:ti,ab

#30 ehdp:ti,ab

#31 ethanehydroxydiphosphonate:ti,ab

#32 "Emoform Total":ti,ab

#33 Eopon:ti,ab

#34 Etidrate:ti,ab

#35 Etidrel:ti,ab

#36 Etidron:ti,ab

#37 Etiplus:ti,ab

#38 Feminoflex:ti,ab

#39 Gen-Eti-Cal:ti,ab

#40 Maxibral:ti,ab

#41 Oflocin:ti,ab

#42 Osfo:ti,ab

#43 Ostedron:ti,ab

#44 Osteodidronel:ti,ab

#45 Osteodrug:ti,ab

#46 Osteoto*:ti,ab

#47 Osteum:ti,ab

#48 Ostogene:ti,ab

#49 Ostopor:ti,ab

#50 Somaflex:ti,ab

#51 Squam:ti,ab

#52 Sterodome:ti,ab

#53 Sviroxit:ti,ab

#54 Tilferan:ti,ab

#55 "Tiloetca Combi":ti,ab

#56 Xidifon:ti,ab

#57 xidiphon*:ti,ab

#58 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57)

#59 (#15 AND #58)

1-2 Search strategies in August 2017

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

Search Strategy:

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1 Osteoporosis, Postmenopausal/ (19613)

2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)

3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)

4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)

5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)

6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)

7 (osteoporo* adj5 menopaus*).tw,kw. (5059)

8 (bone loss* adj5 menopaus*).tw,kw. (1577)

9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)

10 (osteoporo* adj5 age-related).tw,kw. (1080)

11 (bone loss* adj5 age-related).tw,kw. (1567)

12 (osteoporo* adj5 senil*).tw,kw. (1769)

13 (bone loss* adj5 senil*).tw,kw. (50)

14 or/1-13 (42138)

15 Osteoporosis/ (147472)

16 osteoporo*.tw,kw. (179656)

17 Bone Density/ (130889)

18 (bone? adj3 densit*).tw,kw. (122854)

19 bmd.tw,kw. (69978)

20 bone loss*.tw,kw. (59493)

21 or/15-20 (342178)

22 Menopause/ (75006)

23 Postmenopause/ (85192)

24 (postmenopaus* or post-menopaus*).tw,kw. (149132)

25 or/22-24 (214833)

26 21 and 25 (54682)

27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)

28 Etidronic Acid/ (9990)

29 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (29824)

30 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (76319)

31 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (207)

32 or/28-31 [ETIDRONATE] (102208)

33 27 and 32 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3920)

34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1079279)

35 clinical trials as topic.sh. (222303)

36 exp Randomized Controlled Trials as Topic/ (260062)

37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)

38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)

39 trial.ti. (616368)

40 or/34-39 (3364349)

41 33 and 40 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1425)

42 Male/ not (Female/ and Male/) (5256871)

43 41 not 42 [MALE-ONLY REMOVED] (1403)

44 exp Animals/ not (exp Animals/ and Humans/) (15473903)

45 43 not 44 [ANIMAL-ONLY REMOVED] (1342)

46 (comment or editorial or interview or news or newspaper article).pt. (1779415)

47 (letter not (letter and randomized controlled trial)).pt. (1970842)

48 45 not (46 or 47) [OPINION PIECES REMOVED] (1319)

49 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (15974685)

50 48 and 49 (197)

51 50 use ppez [MEDLINE RECORDS] (189)

52 postmenopause osteoporosis/ (13085)

53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (21797)

54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4190)

55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (187)

56 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (197)

57 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (460)

58 (osteoporo* adj5 menopaus*).tw,kw. (5059)

59 (bone loss* adj5 menopaus*).tw,kw. (1577)

60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (428)

61 (osteoporo* adj5 age-related).tw,kw. (1080)

62 (bone loss* adj5 age-related).tw,kw. (1567)

63 (osteoporo* adj5 senil*).tw,kw. (1769)

64 (bone loss* adj5 senil*).tw,kw. (50)

65 or/52-64 (37286)

66 osteoporosis/ (147472)

67 osteoporo*.tw,kw. (179656)

68 bone density/ (130889)

69 (bone? adj3 densit*).tw,kw. (122854)

70 bmd.tw,kw. (69978)

71 bone loss*.tw,kw. (59493)

72 or/66-71 (342178)

73 menopause/ (75006)

74 postmenopause/ (85192)

75 (postmenopaus* or post-menopaus*).tw,kw. (149132)

76 or/73-75 (214833)

77 72 and 76 (54682)

78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (63482)

79 etidronic acid/ (9990)

80 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (29824)

81 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (76319)

82 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (207)

83 or/79-82 [ETIDRONATE] (102208)

84 78 and 83 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3384)

85 randomized controlled trial/ (945706)

86 controlled clinical study/ (447552)

87 exp "clinical trial (topic)"/ (249995)

88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (2589616)

89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (566887)

90 trial.ti. (616368)

91 or/85-90 (3296129)

92 84 and 91 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1204)

93 male/ not (female/ and male/) (5256871)

94 92 not 93 [MALE-ONLY REMOVED] (1188)

95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46851981)

96 exp human/ or exp human experimentation/ or exp human experiment/ (36767051)

97 95 not 96 (10086636)

98 94 not 97 [ANIMAL-ONLY REMOVED] (1179)

99 editorial.pt. (994267)

100 letter.pt. not (letter.pt. and randomized controlled trial/) (1970710)

101 98 not (99 or 100) [OPINION PIECES REMOVED] (1174)

102 (201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc,dd. (33782413)

103 101 and 102 (475)

104 103 use emczd [EMBASE RECORDS] (323)

105 Osteoporosis, Postmenopausal/ (19613)

106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (21797)

107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4190)

108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (187)

109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (197)

110 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (460)

111 (osteoporo* adj5 menopaus*).ti,ab,kw. (5059)

112 (bone loss* adj5 menopaus*).ti,ab,kw. (1577)

113 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (428)

114 (osteoporo* adj5 age-related).ti,ab,kw. (1080)

115 (bone loss* adj5 age-related).ti,ab,kw. (1567)

116 (osteoporo* adj5 senil*).ti,ab,kw. (1769)

117 (bone loss* adj5 senil*).ti,ab,kw. (50)

118 or/105-117 (42138)

119 Osteoporosis/ (147472)

120 osteoporo*.ti,ab,kw. (179656)

121 Bone Density/ (130889)

122 (bone? adj3 densit*).ti,ab,kw. (122853)

123 bmd.ti,ab,kw. (69965)

124 bone loss*.ti,ab,kw. (59493)

125 or/119-124 (342166)

126 Menopause/ (75006)

127 Postmenopause/ (85192)

128 (postmenopaus* or post-menopaus*).ti,ab,kw. (149132)

129 or/126-128 (214833)

130 125 and 129 (54682)

131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (66421)

132 Etidronic Acid/ (9990)

133 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).ti,ab,kw. (10114)

134 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).ti,ab,kw. (67847)

135 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).ti,ab,kw. (57)

136 or/132-135 [ETIDRONATE] (83297)

137 131 and 136 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (2293)

138 Male/ not (Female/ and Male/) (5256871)

139 137 not 138 [MALE-ONLY REMOVED] (2264)

140 ("201112" or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).up. (62320674)

141 139 and 140 (2254)

142 141 use cctr [CENTRAL RECORDS] (217)

143 51 or 104 or 142 [ALL DATABASES] (729)

144 remove duplicates from 143 (606) [TOTAL UNIQUE RECORDS]

145 144 use ppez [MEDLINE UNIQUE RECORDS] (169)

146 144 use emczd [EMBASE UNIQUE RECORDS] (305)

147 144 use cctr [CENTRAL UNIQUE RECORDS] (132)

1-3 Search strategies in June 2019

Date: 2019 Jun 5

Database: Embase Classic+Embase <1947 to 2019 June 04>, Ovid MEDLINE(R) ALL <1946 to June 04, 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <April 2019>

Search Strategy:

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1 Osteoporosis, Postmenopausal/ (19645)

2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (24380)

3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4353)

4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (207)

5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (209)

6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (627)

7 (osteoporo* adj5 menopaus*).tw,kw. (5583)

8 (bone loss* adj5 menopaus*).tw,kw. (1654)

9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (475)

10 (osteoporo* adj5 age-related).tw,kw. (1221)

11 (bone loss* adj5 age-related).tw,kw. (1727)

12 (osteoporo* adj5 senil*).tw,kw. (1864)

13 (bone loss* adj5 senil*).tw,kw. (55)

14 or/1-13 (45303)

15 Osteoporosis/ (158815)

16 osteoporo*.tw,kw. (200650)

17 Bone Density/ (142862)

18 (bone? adj3 densit*).tw,kw. (137288)

19 bmd.tw,kw. (78820)

20 bone loss*.tw,kw. (67392)

21 or/15-20 (379669)

22 Menopause/ (77798)

23 Postmenopause/ (91320)

24 (postmenopaus* or post-menopaus*).tw,kw. (164951)

25 or/22-24 (233689)

26 21 and 25 (59403)

27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (71504)

28 Etidronic Acid/ (10046)

29 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (30324)

30 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (83328)

31 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (221)

32 or/28-31 [ETIDRONATE] (109832)

33 27 and 32 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3992)

34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1128994)

35 clinical trials as topic.sh. (220409)

36 exp Randomized Controlled Trials as Topic/ (295398)

37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (3155455)

38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (665659)

39 trial.ti. (755130)

40 or/34-39 (3965361)

41 33 and 40 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS - RCTS] (1443)

42 Male/ not (Female/ and Male/) (5515219)

43 41 not 42 [MALE-ONLY REMOVED] (1422)

44 exp Animals/ not (exp Animals/ and Humans/) (18276792)

45 43 not 44 [ANIMAL-ONLY REMOVED] (1354)

46 (comment or editorial or interview or news or newspaper article).pt. (1954050)

47 (letter not (letter and randomized controlled trial)).pt. (2094952)

48 45 not (46 or 47) [OPINION PIECES REMOVED] (1333)

49 (2017082* or 201709* or 201710* or 201711* or 201712* or 2018* or 2019*).dt. (2308886)

50 48 and 49 (12)

51 50 use medall [MEDLINE RECORDS] (12)

52 postmenopause osteoporosis/ (13835)

53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (24380)

54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4353)

55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (207)

56 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (209)

57 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (627)

58 (osteoporo* adj5 menopaus*).tw,kw. (5583)

59 (bone loss* adj5 menopaus*).tw,kw. (1654)

60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (475)

61 (osteoporo* adj5 age-related).tw,kw. (1221)

62 (bone loss* adj5 age-related).tw,kw. (1727)

63 (osteoporo* adj5 senil*).tw,kw. (1864)

64 (bone loss* adj5 senil*).tw,kw. (55)

65 or/52-64 (40670)

66 osteoporosis/ (158815)

67 osteoporo*.tw,kw. (200650)

68 bone density/ (142862)

69 (bone? adj3 densit*).tw,kw. (137288)

70 bmd.tw,kw. (78820)

71 bone loss*.tw,kw. (67392)

72 or/66-71 (379669)

73 menopause/ (77798)

74 postmenopause/ (91320)

75 (postmenopaus* or post-menopaus*).tw,kw. (164951)

76 or/73-75 (233689)

77 72 and 76 (59403)

78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (68733)

79 etidronic acid/ (10046)

80 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (30324)

81 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (83328)

82 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (221)

83 or/79-82 [ETIDRONATE] (109832)

84 78 and 83 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3451)

85 randomized controlled trial/ (1037431)

86 controlled clinical study/ (463094)

87 exp "clinical trial (topic)"/ (294922)

88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (3155455)

89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (665659)

90 trial.ti. (755130)

91 or/85-90 (3926497)

92 84 and 91 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1228)

93 male/ not (female/ and male/) (5515219)

94 92 not 93 [MALE-ONLY REMOVED] (1213)

95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (49778412)

96 exp human/ or exp human experimentation/ or exp human experiment/ (39370483)

97 95 not 96 (10409650)

98 94 not 97 [ANIMAL-ONLY REMOVED] (1202)

99 editorial.pt. (1096605)

100 letter.pt. not (letter.pt. and randomized controlled trial/) (2094824)

101 98 not (99 or 100) [OPINION PIECES REMOVED] (1197)

102 (2017082* or 201709* or 201710* or 201711* or 201712* or 2018* or 2019*).dc. (3221271)

103 101 and 102 (3)

104 103 use emczd [EMBASE RECORDS] (3)

105 Osteoporosis, Postmenopausal/ (19645)

106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (24380)

107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4353)

108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (207)

109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (209)

110 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (627)

111 (osteoporo* adj5 menopaus*).ti,ab,kw. (5583)

112 (bone loss* adj5 menopaus*).ti,ab,kw. (1654)

113 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (475)

114 (osteoporo* adj5 age-related).ti,ab,kw. (1221)

115 (bone loss* adj5 age-related).ti,ab,kw. (1727)

116 (osteoporo* adj5 senil*).ti,ab,kw. (1864)

117 (bone loss* adj5 senil*).ti,ab,kw. (55)

118 or/105-117 (45303)

119 Osteoporosis/ (158815)

120 osteoporo*.ti,ab,kw. (200650)

121 Bone Density/ (142862)

122 (bone? adj3 densit*).ti,ab,kw. (137287)

123 bmd.ti,ab,kw. (78807)

124 bone loss*.ti,ab,kw. (67392)

125 or/119-124 (379658)

126 Menopause/ (77798)

127 Postmenopause/ (91320)

128 (postmenopaus* or post-menopaus*).ti,ab,kw. (164951)

129 or/126-128 (233689)

130 125 and 129 (59403)

131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (71504)

132 Etidronic Acid/ (10046)

133 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).ti,ab,kw. (10299)

134 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).ti,ab,kw. (74833)

135 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).ti,ab,kw. (61)

136 or/132-135 [ETIDRONATE] (90570)

137 131 and 136 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (2319)

138 Male/ not (Female/ and Male/) (5515219)

139 137 not 138 [MALE-ONLY REMOVED] (2292)

140 ("201708" or "201709" or "201710" or "201711" or "201712" or 2018* or 2019*).up. (34609819)

141 139 and 140 (1048)

142 141 use cctr [CENTRAL RECORDS] (271)

143 51 or 104 or 142 [ALL DATABASES] (286)

144 remove duplicates from 143 (281) [TOTAL UNIQUE RECORDS]

145 144 use medall [MEDLINE UNIQUE RECORDS] (12)

146 144 use emczd [EMBASE UNIQUE RECORDS] (2)

147 144 use cctr [CENTRAL UNIQUE RECORDS] (267)

1-4 Search strategies in March 2021

Date: 2021 Mar 26

Database: Embase Classic+Embase <1947 to 2021 March 25> , Ovid MEDLINE(R) ALL <1946 to March 25, 2021>, EBM Reviews - Cochrane Central Register of Controlled Trials <February 2021>

Search Strategy:

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1 Osteoporosis, Postmenopausal/ (21108)

2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (26953)

3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4553)

4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (235)

5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (218)

6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (693)

7 (osteoporo* adj5 menopaus*).tw,kw. (6114)

8 (bone loss* adj5 menopaus*).tw,kw. (1753)

9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (496)

10 (osteoporo* adj5 age-related).tw,kw. (1423)

11 (bone loss* adj5 age-related).tw,kw. (1925)

12 (osteoporo* adj5 senil*).tw,kw. (2008)

13 (bone loss* adj5 senil*).tw,kw. (60)

14 or/1-13 (49187)

15 Osteoporosis/ (174101)

16 osteoporo*.tw,kw. (225958)

17 Bone Density/ (158275)

18 (bone? adj3 densit*).tw,kw. (154000)

19 bmd.tw,kw. (89302)

20 bone loss*.tw,kw. (76294)

21 or/15-20 (424390)

22 Menopause/ (82265)

23 Postmenopause/ (99162)

24 (postmenopaus* or post-menopaus*).tw,kw. (180175)

25 or/22-24 (253425)

26 21 and 25 (64508)

27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (77456)

28 Etidronic Acid/ (10315)

29 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (31676)

30 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (91816)

31 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (251)

32 or/28-31 [ETIDRONATE] (119619)

33 27 and 32 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (4104)

34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1217438)

35 clinical trials as topic.sh. (228500)

36 exp Randomized Controlled Trials as Topic/ (353615)

37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (3697695)

38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (750801)

39 trial.ti. (914879)

40 or/34-39 (4565827)

41 33 and 40 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1472)

42 Male/ not (Female/ and Male/) (5975933)

43 41 not 42 [MALE-ONLY REMOVED] (1451)

44 exp Animals/ not (exp Animals/ and Humans/) (19238236)

45 43 not 44 [ANIMAL-ONLY REMOVED] (1380)

46 (comment or editorial or interview or news or newspaper article).pt. (2215886)

47 (letter not (letter and randomized controlled trial)).pt. (2297267)

48 45 not (46 or 47) [OPINION PIECES REMOVED] (1359)

49 (201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).dt. (2593755)

50 48 and 49 (10)

51 50 use medall [MEDLINE RECORDS] (10)

52 postmenopause osteoporosis/ (14694)

53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (26953)

54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4553)

55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (235)

56 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (218)

57 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (693)

58 (osteoporo* adj5 menopaus*).tw,kw. (6114)

59 (bone loss* adj5 menopaus*).tw,kw. (1753)

60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (496)

61 (osteoporo* adj5 age-related).tw,kw. (1423)

62 (bone loss* adj5 age-related).tw,kw. (1925)

63 (osteoporo* adj5 senil*).tw,kw. (2008)

64 (bone loss* adj5 senil*).tw,kw. (60)

65 or/52-64 (44280)

66 osteoporosis/ (174101)

67 osteoporo*.tw,kw. (225958)

68 bone density/ (158275)

69 (bone? adj3 densit*).tw,kw. (154000)

70 bmd.tw,kw. (89302)

71 bone loss*.tw,kw. (76294)

72 or/66-71 (424390)

73 menopause/ (82265)

74 postmenopause/ (99162)

75 (postmenopaus* or post-menopaus*).tw,kw. (180175)

76 or/73-75 (253425)

77 72 and 76 (64508)

78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (74528)

79 etidronic acid/ (10315)

80 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (31676)

81 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (91816)

82 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (251)

83 or/79-82 [ETIDRONATE] (119619)

84 78 and 83 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3552)

85 randomized controlled trial/ (1183318)

86 controlled clinical study/ (467757)

87 exp "clinical trial (topic)"/ (352349)

88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (3697695)

89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (750801)

90 trial.ti. (914879)

91 or/85-90 (4534818)

92 84 and 91 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1255)

93 male/ not (female/ and male/) (5975933)

94 92 not 93 [MALE-ONLY REMOVED] (1240)

95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (54340256)

96 exp human/ or exp human experimentation/ or exp human experiment/ (43297718)

97 95 not 96 (11044416)

98 94 not 97 [ANIMAL-ONLY REMOVED] (1230)

99 editorial.pt. (1253326)

100 letter.pt. not (letter.pt. and randomized controlled trial/) (2297113)

101 98 not (99 or 100) [OPINION PIECES REMOVED] (1225)

102 (201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).dc. (3843046)

103 101 and 102 (10)

104 103 use emczd [EMBASE RECORDS] (10)

105 Osteoporosis, Postmenopausal/ (21108)

106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (26953)

107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4553)

108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (235)

109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (218)

110 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (693)

111 (osteoporo* adj5 menopaus*).ti,ab,kw. (6114)

112 (bone loss* adj5 menopaus*).ti,ab,kw. (1753)

113 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (496)

114 (osteoporo* adj5 age-related).ti,ab,kw. (1423)

115 (bone loss* adj5 age-related).ti,ab,kw. (1925)

116 (osteoporo* adj5 senil*).ti,ab,kw. (2008)

117 (bone loss* adj5 senil*).ti,ab,kw. (60)

118 or/105-117 (49187)

119 Osteoporosis/ (174101)

120 osteoporo*.ti,ab,kw. (225958)

121 Bone Density/ (158275)

122 (bone? adj3 densit*).ti,ab,kw. (153999)

123 bmd.ti,ab,kw. (89286)

124 bone loss*.ti,ab,kw. (76294)

125 or/119-124 (424376)

126 Menopause/ (82265)

127 Postmenopause/ (99162)

128 (postmenopaus* or post-menopaus*).ti,ab,kw. (180175)

129 or/126-128 (253425)

130 125 and 129 (64508)

131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (77456)

132 Etidronic Acid/ (10315)

133 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).ti,ab,kw. (10741)

134 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).ti,ab,kw. (83123)

135 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).ti,ab,kw. (67)

136 or/132-135 [ETIDRONATE] (99421)

137 131 and 136 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (2347)

138 Male/ not (Female/ and Male/) (5975933)

139 137 not 138 [MALE-ONLY REMOVED] (2319)

140 (201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).up. (37510586)

141 139 and 140 (1055)

142 141 use cctr [CENTRAL RECORDS] (235)

143 51 or 104 or 142 [ALL DATABASES] (255)

144 remove duplicates from 143 (253) [TOTAL UNIQUE RECORDS]

145 144 use medall [MEDLINE UNIQUE RECORDS] (10)

146 144 use emczd [EMBASE UNIQUE RECORDS] (9)

147 144 use cctr [CENTRAL UNIQUE RECORDS] (234)

1-5 Search strategies in February 2023

Date: 2023 Feb 01

Database: Embase Classic+Embase <1947 to 2023 February 01>, Ovid MEDLINE(R) ALL <1946 to February 01, 2023>, EBM Reviews - Cochrane Central Register of Controlled Trials <January 2023>

Search Strategy:

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1 Osteoporosis, Postmenopausal/ (23449)

2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (28795)

3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4632)

4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (254)

5 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (224)

6 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (306)

7 (osteoporo* adj5 menopaus*).tw,kw. (6717)

8 (bone loss* adj5 menopaus*).tw,kw. (1816)

9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (355)

10 (osteoporo* adj5 age-related).tw,kw. (1626)

11 (bone loss* adj5 age-related).tw,kw. (2040)

12 (osteoporo* adj5 senil*).tw,kw. (2150)

13 (bone loss* adj5 senil*).tw,kw. (74)

14 or/1-13 (52501)

15 Osteoporosis/ (191120)

16 osteoporo*.tw,kw. (249824)

17 Bone Density/ (175474)

18 (bone? adj3 densit*).tw,kw. (166512)

19 bmd.tw,kw. (98261)

20 bone loss*.tw,kw. (84734)

21 or/15-20 (467674)

22 Menopause/ (88704)

23 Postmenopause/ (108025)

24 (postmenopaus* or post-menopaus*).tw,kw. (194232)

25 or/22-24 (273039)

26 21 and 25 (68864)

27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (82618)

28 Etidronic Acid/ (10567)

29 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (33247)

30 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (100303)

31 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (277)

32 or/28-31 [ETIDRONATE] (129695)

33 27 and 32 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (4272)

34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (676928)

35 clinical trials as topic.sh. (237785)

36 exp Randomized Controlled Trials as Topic/ (449683)

37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (4146708)

38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (813329)

39 trial.ti. (1060094)

40 or/34-39 (4917554)

41 33 and 40 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1508)

42 Male/ not (Female/ and Male/) (6441071)

43 41 not 42 [MALE-ONLY REMOVED] (1489)

44 exp Animals/ not (exp Animals/ and Humans/) (17496776)

45 43 not 44 [ANIMAL-ONLY REMOVED] (1427)

46 (comment or editorial or interview or news or newspaper article).pt. (2436688)

47 (letter not (letter and randomized controlled trial)).pt. (2494407)

48 45 not (46 or 47) [OPINION PIECES REMOVED] (1406)

49 (20210325* or "20210326" or "20210327" or "20210328" or "20210329" or 2021033* or 202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022* or 2023*).dt. (3012575)

50 48 and 49 (18)

51 50 use medall [MEDLINE RECORDS] (18)

52 postmenopause osteoporosis/ (15536)

53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (28795)

54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4632)

55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (254)

56 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (224)

57 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (306)

58 (osteoporo* adj5 menopaus*).tw,kw. (6717)

59 (bone loss* adj5 menopaus*).tw,kw. (1816)

60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (355)

61 (osteoporo* adj5 age-related).tw,kw. (1626)

62 (bone loss* adj5 age-related).tw,kw. (2040)

63 (osteoporo* adj5 senil*).tw,kw. (2150)

64 (bone loss* adj5 senil*).tw,kw. (74)

65 or/52-64 (47160)

66 osteoporosis/ (191120)

67 osteoporo*.tw,kw. (249824)

68 bone density/ (175474)

69 (bone? adj3 densit*).tw,kw. (166512)

70 bmd.tw,kw. (98261)

71 bone loss*.tw,kw. (84734)

72 or/66-71 (467674)

73 menopause/ (88704)

74 postmenopause/ (108025)

75 (postmenopaus* or post-menopaus*).tw,kw. (194232)

76 or/73-75 (273039)

77 72 and 76 (68864)

78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (79475)

79 etidronic acid/ (10567)

80 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).tw,kw,rn. (33247)

81 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).tw,kw,rn. (100303)

82 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).tw,kw,rn. (277)

83 or/79-82 [ETIDRONATE] (129695)

84 78 and 83 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3682)

85 randomized controlled trial/ (1348144)

86 controlled clinical study/ (468213)

87 exp "clinical trial (topic)"/ (421506)

88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (4146708)

89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (813329)

90 trial.ti. (1060094)

91 or/85-90 (5052741)

92 84 and 91 [ETIDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1312)

93 male/ not (female/ and male/) (6441071)

94 92 not 93 [MALE-ONLY REMOVED] (1297)

95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (59613925)

96 exp human/ or exp human experimentation/ or exp human experiment/ (47911414)

97 95 not 96 (11704582)

98 94 not 97 [ANIMAL-ONLY REMOVED] (1287)

99 editorial.pt. (1393619)

100 letter.pt. not (letter.pt. and randomized controlled trial/) (2487960)

101 98 not (99 or 100) [OPINION PIECES REMOVED] (1282)

102 (20210325* or "20210326" or "20210327" or "20210328" or "20210329" or 2021033* or 202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022* or 2023*).dc. (3942137)

103 101 and 102 (8)

104 103 use emczd [EMBASE RECORDS] (8)

105 Osteoporosis, Postmenopausal/ (23449)

106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (28795)

107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4632)

108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (254)

109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (224)

110 (osteoporo* adj5 "after" adj5 menopaus*).tw,kw. (306)

111 (osteoporo* adj5 menopaus*).ti,ab,kw. (6717)

112 (bone loss* adj5 menopaus*).ti,ab,kw. (1816)

113 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (355)

114 (osteoporo* adj5 age-related).ti,ab,kw. (1626)

115 (bone loss* adj5 age-related).ti,ab,kw. (2040)

116 (osteoporo* adj5 senil*).ti,ab,kw. (2150)

117 (bone loss* adj5 senil*).ti,ab,kw. (74)

118 or/105-117 (52501)

119 Osteoporosis/ (191120)

120 osteoporo*.ti,ab,kw. (249824)

121 Bone Density/ (175474)

122 (bone? adj3 densit*).ti,ab,kw. (166511)

123 bmd.ti,ab,kw. (98243)

124 bone loss*.ti,ab,kw. (84734)

125 or/119-124 (467658)

126 Menopause/ (88704)

127 Postmenopause/ (108025)

128 (postmenopaus* or post-menopaus*).ti,ab,kw. (194232)

129 or/126-128 (273039)

130 125 and 129 (68864)

131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (82618)

132 Etidronic Acid/ (10567)

133 (etidronate or editronic acid or anfozan or biotredine or bonemass or dequest or detidron or diadronel or didrocal or didrokit or didro kit or didronal or didronat* or didronel or difosfen or dinol or diphos or diphosphonate or dralen or dronate-os).ti,ab,kw. (11047)

134 (ehdp or ethanehydroxydiphosphonate or emoform total or eopon or etibon or etidrate or etidrel or etidron or etiplus or feminoflex or gen-eti-cal or hedp or maxibral or oflocin or osfo or ostedron or osteodidronel or osteodrug or osteoto* or osteum or ostogene or ostopor).ti,ab,kw. (91457)

135 (somaflex or squam or sterodome or sviroxit or tilferan or tiloetca combi or turpinal or xidifon or xidiphon*).ti,ab,kw. (66)

136 or/132-135 [ETIDRONATE] (108201)

137 131 and 136 [ETIDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (2419)

138 Male/ not (Female/ and Male/) (6441071)

139 137 not 138 [MALE-ONLY REMOVED] (2389)

140 (202103* or 202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022* or 2023*).up. (39978501)

141 139 and 140 (1094)

142 141 use cctr [CENTRAL RECORDS] (313)

143 51 or 104 or 142 [ALL DATABASES] (339)

144 remove duplicates from 143 (333) [TOTAL UNIQUE RECORDS]

145 144 use medall [MEDLINE UNIQUE RECORDS] (17)

146 144 use emczd [EMBASE UNIQUE RECORDS] (7)

147 144 use cctr [CENTRAL UNIQUE RECORDS] (309)

Appendix 2. Models for fracture risk in postmenopausal women: FRACTURE index

Table 1. FRACTURE Index* questions and scoring

Questions		Point Score
1. What is your current age?	Less than 65	0
	65–69	1
	70–74	2
	75–79	3
	80–84	4
	85 or older	5
2. Have you broken any bones after age 50?	Yes	1
	No / Don't know	0
3. Has your mother had a hip fracture after age 50?	Yes	1
	No / Don't know	0
4. Do you weigh 125 pounds or less?	Yes	1
	No	0
5. Are you currently a smoker?	Yes	1
	No	0
6. Do you usually need to use your arms to assist yourself in standing up from a chair?	Yes	1
	No / Don't know	0
If you have a current bone density (BMD) assessment, then answer next question.		
7. BMD results: Total Hip T-score	≥ 1	0
	-1 to -2	2
	-2 to -2.5	3
	<-2.5	4

* From Black 2001 [Black 2001].

Table 2. Five-year risk of fracture by quintiles of the FRACTURE Index*: assessment with bone mineral density

FRACTURE Index	Risk of fractures (%)		
	Vertebral	Non-vertebral	Hip
1-2	1.2	8.6	0.4

(Continued)

3-4	2.5	13.1	0.9
5	5.3	16.5	1.9
6-7	7.1	19.8	3.9
8-13	11.2	27.5	8.7

* From Black 2001 [Black 2001].

Appendix 3. Estimated five-year age-specific risks* of first and subsequent osteoporotic fractures

Age (years)	Spine		Hip		Other†	
	First	Subsequent	First	Subsequent	First	Subsequent
50-54	0.2	0.5	0.0	0.0	1.6	2.6
55-59	0.4	4.0	0.2	0.4	2.1	3.4
60-64	1.0	9.7	0.2	0.2	3.1	6.2
65-69	1.5	14.3	0.8	0.9	4.2	8.4
70-74	1.8	17.2	1.6	2.2	6.5	11.2
75-79	3.3	24.2	3.8	5.2	7.4	12.0
80-84	2.3	19.1	7.1	9.2	10.3	15.9
85-89	2.5	20.9	16.7	20.1	13.5	18.4
90+	4.7	27.9	20.9	22.8	35.2	37.7

*From Doherty 2001 [Doherty 2001]
†Other: non-vertebral, including wrist, forearm, humerus, tibia/fibula, pelvis, ribs, femur but exclude hip

Appendix 4. List and management of the eligible studies excluded from the quantitative synthesis

List of the four eligible studies not included in the quantitative synthesis

Author year	Excerpts relevant to outcomes of interest	Reasons for not including study in the quantitative synthesis
Primary prevention (one study)		
Evans 1993	"Thirty-six healthy women completed the 2-year study, out of an initial 46. Reasons for withdrawal were: non-compliance (4), decision to commence hormone replacement ther-	1. For withdrawals due to adverse events: data were not reported by groups.

(Continued)

	apy (3), concern about low bone mass (1), calcium supplement thought to cause bone pain (2)." "...those taking etidronate complained of mild diarrhoea (7), nausea and heartburn (7), hip pain (1), constipation (1), leg cramps (1), or skin rash (1). The calcium supplement was said to cause indigestion (3), constipation (2), or dry mouth (1). The phosphate supplements were associated with mild nausea (3) and diarrhoea (5). "	2. For gastrointestinal adverse events, data were reported as the numbers of gastrointestinal events, which could not be summed up to the number of participants sustaining at least one of the events. In addition, data were not reported by groups.
Secondary prevention (three studies)		
Hasling 1994	"No significant changes in height were detected in any group, although new spinal fractures occurred in all groups… The overall number of new fractures was small and no significant difference in fracture rate could be demonstrated between the groups. The small number of patients entering the different groups made demonstration of different fracture rates very unlikely." "Two patients dropped out after 30 and 45 weeks because they could not bear regular bleeds; the other 4 drop-outs were not drug related."	1. Narrative descriptions were related to radiographic vertebral and non-vertebral fractures. However, the data (number of participants sustaining the event) were not provided. 2. For withdrawals due to adverse events: data were not extractable because they were not reported by groups. In addition, we did not know whether the "not drug-related" withdrawals were adverse events.
Hu 2005	"The total score of QOL [quality of life] and the score of disease domain and physical domain of the HRT [hormone replacement] therapy group and risedronate therapy group were higher than the placebo therapy group (F = 17.335, P < 0. 001), but the vitamin D addition calcium therapy group was not different from that of the placebo therapy group."	The QOL total scores for four groups were only reported at 12 months after the treatment, of which one group (HRT group, in Table 1) apparently had incorrect score. None of the changes in the total scores of the four groups were extractable.
Pacifici 1988	In Table 2, new radiographic vertebral fractures were reported (mean ± standard deviation) for three arms: 0.25 ± 0.46 in calcium group (n = 15), 0.30 ± 0.40 in ADFR with calcium group (n = 16) and 0.25 ± 0.46 in oestrogen-progesterone with calcium group (n = 19).	Only the total numbers of fractures can be calculated, which is not usable for quantitative synthesis (number of participants sustaining a fracture).

Appendix 5. Relative risk of clinical vertebral, non-vertebral, hip, and wrist fractures after etidronate (or combination) versus active drug: secondary prevention

Intervention: etidronate	Comparators	No. of studies	Number of women with events/ number of women		Relative risk (95% CI)
			Intervention	Comparator	
Clinical vertebral fractures					
400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Intermittent/cyclic clodronate	1	0 / 31	0 / 38	NE
Non-vertebral fractures					

(Continued)

400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Intermittent/cyclic clodronate	1	0 / 31	0 / 8	NE
	Fluoride 50 mg/day	1	6 / 47	6 / 31	0.66 (0.23,1.86)
	HRT	1	1 / 17	1 / 18	1.06 (0.07, 15.62)
	(Etidronate 400 mg/day + HRT)	1	1 / 17	1 / 19	1.12 (0.08, 16.52)
200 mg/day	Alendronate 5 mg/day	1	0 / 25	0 / 25	NE
	Risedronate 2.5 mg/day	1	4 / 117	7 / 118	0.58 (0.17,1.92)
	Alfacalcidol 1 µg/day	1	1 / 66	1 / 66	1.00 (0.06,15.65)
	Calcitonin 20 IU/week, IV	1	1 / 66	0 / 66	3.00 (0.12,72.33)
	HRT	1	1 / 66	0 / 66	3.00 (0.12,72.33)
	Menatetrenone 45 mg/day	1	1 / 66	0 / 66	3.00 (0.12,72.33)
(400 mg/day + HRT)	Placebo	1	1 / 19	1 / 18	0.95 (0.06,14.04)
	HRT	1	1 / 19	1 / 18	0.95 (0.06,14.04)
Hip and wrist fractures					
400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Intermittent/cyclic clodronate	1	0 / 31	0 / 8	NE
200 mg/day	Alendronate 5 mg/day	1	0 / 25	0 / 25	NE
	Alfacalcidol 1 µg/day	1	0 / 66	0 / 66	NE
	Calcitonin 20 IU/week, IV	1	0 / 66	0 / 66	NE
	HRT	1	0 / 66	0 / 66	NE
	Menatetrenone 45 mg/day	2	0 / 91	0 / 89	NE
			- 0/66	- 0/66	NE
			- 0/25	- 0/23	NE
	(Etidronate 200 mg/day + Alfacalcidol 1 µg/day)	1	0 / 20	0 / 20	NE

Route of drug administration: unless otherwise specified, drugs were administered orally.

CI: confidence interval; **HRT:** hormone replacement therapy; **IV:** intravenous; **NE:** not estimable.

Appendix 6. Relative risk of withdrawals due to adverse events and serious adverse events after etidronate (or combination) versus active drug

Intervention: etidronate	Comparators	No. of Studies	Number of women with events/ number of women		Relative risk (95% CI)
			Intervention	Comparator	
Withdrawals due to adverse events. Primary prevention					
400 mg/day	HRT	1	2 / 14	2 / 15	1.07 (0.17,6.61)
	(Etidronate 400 mg/day + HRT)	1	2 / 14	2 / 15	1.07 (0.17,6.61)
400 mg/day + HRT	Placebo	1	2 / 15	3 / 14	0.62 (0.12,3.19)
	HRT	1	2 / 15	2 / 15	1.00 (0.16,6.20)
Withdrawals due to adverse events. Secondary prevention					
400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Alendronate 10 mg/day	2	0 / 58	9 / 61	***0.11 (0.01,0.79)***
			- 0 /22	- 3 / 24	
			- 0 / 36	- 6 / 37	
	Intermittent/cyclic alendronate 10 mg/day	2	0 / 58	1 / 57	0.31 (0.01,7.27)
			- 0 / 22	- 0 / 24	
			- 0 / 36	- 1 / 33	
	Intermittent/cyclic clodronate	1	0 / 31	0 / 8	NE
	Calcitriol 0.5 µg/day	1	0 / 36	1 / 34	0.32 (0.01,7.48)
	Fluoride 50 mg/day	1	3 / 63	13 / 55	***0.20 (0.06,0.67)***
	HRT	1	3 / 17	3 / 18	1.06 (0.25, 4.54)
	(Etidronate 400 mg/day + calcitriol 0.5 µg/day)	1	5 / 28	4 / 30	1.34 (0.40,4.49)
	(Etidronate 400 mg/day + HRT)	1	3 / 17	4 / 19	0.84 (0.22, 3.22)
200 mg/day	Alendronate 5 mg/day	1	0 / 25	0 / 25	NE
	Risedronate 2.5 mg/day	1	7 / 117	8 / 118	0.88 (0.33,2.36)
	Alfacalcidol 1 µg/day	1	1 / 66	0 / 66	3.00 (0.12,72.33)
	Calcitonin 20 IU/week, IV	1	1 / 66	0 / 66	3.00 (0.12,72.33)
	HRT	1	1 / 66	3 / 66	0.33 (0.04,3.12)

(Continued)

	Menatetrenone 45 mg/day	1	1 / 66	0 / 66	3.00 (0.12,72.33)
	(Etidronate 200 mg/day + alfacalcidol 1 µg/day)	1	0 / 20	0 / 20	NE
400 mg/day + Calcitriol 0.5 µg/day	Calcitriol 0.5 µg/day	1	0 / 10	0 / 10	NE
	(Calcitonin 100 IU/2 days, IN + calcitriol 0.25 µg/day)	1	0 / 10	0 / 10	NE
400 mg/day + HRT	Placebo	1	4 / 19	3 / 18	1.26 (0.33,4.88)
	HRT	1	4 / 19	3 / 18	1.26 (0.33,4.88)
Serious adverse events. Secondary prevention					
400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Intermittent/cyclic clodronate	1	0 / 31	0 / 8	NE
	ADFR*	1	0 / 19	0 / 18	NE
200 mg/day	Alendronate 5 mg/day	1	0 / 25	0 / 25	NE

*ADFR: Triiodothyronine 100 µg/day for 7 days, followed by oral etidronate 400 mg/day for 2 weeks; the drug-free period until next activation was 12 weeks. The 15-week treatment cycle was then repeated four times.

Route of drug administration: unless otherwise specified, drugs were administered orally.

ADFR: repeated cycle of activation, depression, free, and repeat; **CI:** confidence interval; **HRT:** hormone replacement therapy; **IN:** intranasal; **IU:** international unit; **IV:** intravenous; **NE:** not estimable

Appendix 7. Relative risk of minor outcomes after etidronate (or combination) versus active drug: secondary prevention

Intervention: etidronate	Comparators	No. of Studies	Number of women with events/ Number of women		Relative risk (95% CI)
			Intervention	Comparator	
Radiographic vertebral fractures					
400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Intermittent/cyclic clodronate	1	0 / 31	0 / 8	NE
	Fluoride 50 mg/day	1	8 / 47	5 / 31	1.06 (0.38,2.93)
	HRT	1	3 / 17	2 / 18	1.59 (0.30, 8.37)
	(Etidronate 400 mg/day + HRT)	1	3 / 17	1 / 19	3.35 (0.38, 29.26)
200 mg/day	Alendronate 5 mg/day	1	0 / 25	0 / 25	NE

(Continued)

	Risedronate 2.5 mg/day	1	2 / 106	0 / 101	4.77 (0.23,98.08)
	Alfacalcidol 1 µg/day	1	8 / 66	11 / 66	0.73 (0.31,1.69)
	Calcitonin 20 IU/week, IV	1	8 / 66	8 / 66	1.00 (0.40,2.51)
	HRT	1	8 / 66	7 / 66	1.14 (0.44,2.97)
	Menatetrenone 45 mg/day	2	10 / 91	11 / 89	0.89 (0.40,2.00)
			- 8/66	- 9/66	
			- 2/25	- 2/23	
	(Etidronate 200 mg/day + alfacalcidol 1 µg/day)	1	1 / 20	1 / 20	1.00 (0.07,14.90)
400 mg/day + HRT	Placebo	1	1 / 19	5 / 18	0.19 (0.02,1.47)
	HRT	1	1 / 19	2 / 18	0.47 (0.05,4.78)
Gastrointestinal adverse events					
400 mg/day	ADFR*	1	2 / 19	0 / 18	4.75 (0.24,92.65)
	Fluoride 50 mg/day	1	10 / 47	12 / 31	0.55 (0.27,1.11)
200 mg/day	Alendronate 5 mg/day	1	2 / 25	1 / 25	2.00 (0.19,20.67)
	Risedronate 2.5 mg/day	1	23 / 117	27 / 118	0.86 (0.52,1.41)
	Menatetrenone 45 mg/day	1	5 / 25	0 / 23	10.15 (0.59,174.03)
	(Etidronate 200 mg/day + alfacalcidol 1 µg/day)	1	0 / 20	0 / 20	1.00 (0.07,14.90)
Atypical femoral fracture					
400 mg/day	Alendronate 5 mg/day	1	0 / 31	0 / 38	NE
	Intermittent/cyclic clodronate	1	0 / 31	0 / 8	NE
200 mg/day	Alfacalcidol 1 µg/day	1	0 / 66	0 / 66	NE
	Calcitonin 20 IU/week, IV	1	0 / 66	0 / 66	NE
	HRT	1	0 / 66	0 / 66	NE
	Menatetrenone 45 mg/day	2	0 / 91	0 / 89	NE
			- 0 / 66	- 0 / 66	
			- 0 / 25	- 0 / 23	

Route of drug administration: unless otherwise specified, drugs were administered orally.

ADFR: repeated cycle of activation, depression, free, and repeat; **CI:** confidence interval; **HRT:** hormone replacement therapy; **IV:** intravenous; **NE:** not estimable

*ADFR: triiodothyronine 100 µg/day for 7 days, followed by oral etidronate 400 mg/day for 2 weeks and drug-free period for 12 weeks until next activation. The 15-week treatment cycle was then repeated four times.

WHAT'S NEW

Date	Event	Description
5 April 2024	New search has been performed	We updated the literature search on 26 March 2021 and 1 February 2023. One new study not reporting outcome data was identified.
5 April 2024	New citation required but conclusions have not changed	New citation required but conclusions have not changed

HISTORY

Review first published: Issue 3, 2001

Date	Event	Description
13 January 2021	New search has been performed	Updated review for editorial review
13 January 2021	New citation required and conclusions have changed	Updated search strategies with a broader scope
13 August 2008	Amended	Absolute event rates included in the Plain language summary.
28 May 2008	Amended	Converted to new review format. CMSG ID C033-R
14 November 2007	New citation required and conclusions have changed	See published notes for details on update.

CONTRIBUTIONS OF AUTHORS

George Wells (GW) was involved in the conception, design, and implementation of the project, as well as the review of the final report.

Shu-Ching Hsieh (SH) was the joint first author who developed the conception and methodology of the review, conducted literature screening and study selection, data abstraction and analysis, risk of bias assessment, interpretation, and writing of the final report.

Joan Peterson (JP) was involved in the conception and design of the review, literature screening and study selection for the 2021 updated search, and contributed to the writing and amendments of the final review.

Carine Zheng (CZ) was involved with the conception of the review, literature screening and study selection, data abstraction, and risk of bias assessment.

Shannon Kelly (SK) was involved in the conception and design of the review, commented on the implementation process, and reviewed of the final report.

Beverley Shea made important comments on the conduct of the review and reviewed the final report.

Peter Tugwell provided clinical rheumatology expertise and methodological guidance.

DECLARATIONS OF INTEREST

None at present.

This review was updated without the support of any industry sponsor.

SOURCES OF SUPPORT

Internal sources

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External sources

- Drug Safety and Effectiveness Network, Canadian Institutes of Health Research (in part)., Canada

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to the changes made in accordance with the updated Cochrane review methodologies (Deeks 2022), there are seven main differences between this review update and the previous version of the review (Wells 2008a), as follows.

1) We included articles published after the previous review was completed (updated to 01 February 2023).

2) We included all active-controlled trials of etidronate in addition to those that were placebo-controlled.

3) Following the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards (Higgins 2022), we included all participant-, intervention- and comparator-eligible studies, whether or not they reported our outcomes of interest.

4) We refined the definitions for primary and secondary prevention and developed a peer-reviewed hierarchical algorithm via consensus. Major changes in classification included a lower bone mineral density (BMD) cut-off value (2.5 versus 2 standard deviations (SDs)), an older age limit (75 versus 62 years), and the elimination of the 20% baseline fracture criteria (Figure 1).

5) We divided vertebral fractures into clinical and radiographic/ morphometric, since the two are not always synonymous. For example, Greenspan 2001 found that 18.3% of 482 asymptomatic (had no prior knowledge of vertebral fractures) postmenopausal women, had vertebral fractures determined by dual energy X-ray absorptiometry. The Fracture Intervention Study (6084 women with available spinal radiographs) observed a discrepancy between incident vertebral fractures first identified through radiographic evidence versus patients' symptomatology (e.g. back pain). Only 22.6% (101/446) of radiographic vertebral deformities had been clinically diagnosed, although this proportion was increased for more severe deformities. On the other hand, most of the clinical fractures could be classified as severe, but 21.7% did not even meet the most liberal morphometric criterion (Fink 2005). This update review explicitly counted each type of vertebral fracture with defined criteria.

6) We added health-related quality of life as an outcome to measure etidronate's effects from patients' perspective. For safety outcomes, the current review added serious adverse events, gastrointestinal adverse events, acute phase reaction, osteonecrosis of the jaw, atypical femoral fractures, and atrial fibrillation to the quantitative analyses. This is in contrast to the previous review, in which safety outcomes other than withdrawals due to adverse events were only presented descriptively.

7) We made a number of changes to our analyses. We included cyclic etidronate 200 mg/day as a base case analysis versus a subgroup analysis, in addition to the 400 mg/day dose. We also added one subgroup analysis to investigate the effect of prior bisphosphonate experience. For sensitivity analyses, we deleted two and added another three testing variables to test the robustness of the results of the base case analysis. We removed the random-effects versus fixed-effect comparison because the circumstances under which one or the other would be used were clearly described and, in the previous review, the results obtained from the two models were similar. We removed the sensitivity analyses testing different baseline vertebral fracture rates to define a secondary prevention study (i.e. 100%, > 80%, > 60%, > 40%, > 20%) because the cut-off percentage of baseline vertebral fracture was not included in the hierarchical classification algorithm. We added three sensitivity analyses: (a) including only studies with fractures measured as an efficacy outcome; (b) excluding studies classified as primary/secondary prevention based only on age; and (c) excluding studies applying an ADFR (activation, depression, free, repeat) regimen from the base case analysis. Finally, we used follow-up denominators (the number of participants assessed for that outcome) as our study numbers (Ns) and conducted a sensitivity analysis using the baseline (randomized) denominators. For comparisons that included studies reporting zero events for both treatment and control, we calculated the Peto odds ratio (POR), in addition to the relative risk (RR). If both effect measures provided similar results, we presented the RR due to its superiority in interpreting comparative effectiveness and safety.

NOTES

This review updates a previously published review of etidronate conceived, conducted, and completed, in part, by the authors of this report (Cranney 2001; Wells 2008a). Given the expanded review scope, our updated literature search retrieved an additional 16 trials

with pair-wise comparisons of cyclic etidronate versus placebo or other anti-osteoporotic drugs, including five primary prevention trials (Adami 2000; Chilibeck 2002; Heath 2000; Tobias 1997; Wimalawansa 1995) and 11 secondary prevention trials (Fukunaga 2002; Guañabens 2000; Gürlek 1997; Iwamoto 2001; Iwamoto 2003b; Iwamoto 2005; Köşüş 2005; Masud 1998; Russo 1996; Sahota 2000; Steiniche 1991). One study included in the previous review was found to report fractures by event numbers instead of incidence (number of women sustaining a fracture), so it was excluded from the synthesis (Pacifici 1988). All the five primary prevention studies compared etidronate with placebo, with one also reporting an active comparison of etidronate with another active agent (Wimalawansa 1995). However, all the 11 secondary prevention trials investigated etidronate's head-to-head comparisons with other anti-osteoporotic agents except for one 3-arm trial (Iwamoto 2001), which investigated the effects of etidronate 200 mg/day versus placebo.

In summary, the conclusions are similar in this review and both of the previous two reviews. Etidronate is observed to make little or no difference to all the benefit and harm outcomes. The only exception is for the secondary prevention of radiographic vertebral fractures, however, which was supported by evidence with very low certainty. We don't know whether etidronate reduces radiographic vertebral fractures.

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium; Etidronic Acid [therapeutic use]; *Hip Fractures; *Osteoporosis [drug therapy]; *Osteoporotic Fractures [chemically induced] [drug therapy] [prevention & control]; Postmenopause; Secondary Prevention; *Spinal Fractures [prevention & control]; Vitamin D; *Wrist Fractures; *Wrist Injuries [chemically induced] [drug therapy]

MeSH check words

Female; Humans