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

Wells GA, Hsieh SC, Zheng C, Peterson J, Liu W, Kelly SE, Tugwell P

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[Intervention Review]

# Risedronate 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. Risedronate belongs to the bisphosphonate class of drugs which act to inhibit bone resorption by interfering with the activity of osteoclasts. This is an update of a Cochrane Review that was originally published in 2003.

### Objectives

We assessed the benefits and harms of risedronate in the primary and secondary prevention of osteoporotic fractures for postmenopausal women at lower and higher risk for fractures, respectively.

### Search methods

With broader and updated strategies, we searched the Cochrane Central Register of Control Trials (CENTRAL), MEDLINE and Embase. A grey literature search, including the online databases ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), and drug approval agencies, as well as bibliography checks of relevant systematic reviews was also performed. Eligible trials published between 1966 to 24 March 2021 were identified.

### Selection criteria

We included randomised controlled trials that assessed the benefits and harms of risedronate in the prevention of fractures for postmenopausal women. Participants must have received at least one year of risedronate, placebo or other anti-osteoporotic drugs, with or without concurrent calcium/vitamin D. Major outcomes were clinical vertebral, non-vertebral, hip and wrist fractures, withdrawals due to adverse events, and serious adverse events. In the interest of clinical relevance and applicability, we classified a study as secondary prevention if its population fulfilled more than one of the following hierarchical criteria: a diagnosis of osteoporosis, a history of vertebral fractures, low bone mineral density (BMD)T score ≤ -2.5, and age ≥ 75 years old. If none of these criteria was met, the study was considered to be primary prevention.

### Data collection and analysis

We used standard methodology expected by Cochrane. We pooled the relative risk (RR) of fractures using a fixed-effect model based on the expectation that the clinical and methodological characteristics of the respective primary and secondary prevention studies would be homogeneous, and the experience from the previous review suggesting that there would be a small number of studies. The base case

included the data available for the longest treatment period in each placebo-controlled trial and a >15% relative change was considered clinically important. The main findings of the review were presented in summary of findings tables, using the GRADE approach.

In addition, we looked at benefit and harm comparisons between different dosage regimens for risedronate and between risedronate and other anti-osteoporotic drugs.

**Main results**

Forty-three trials fulfilled the eligibility criteria, among which 33 studies (27,348 participants) reported data that could be extracted and quantitatively synthesized. We had concerns about particular domains of risk of bias in each trial. Selection bias was the most frequent concern, with only 24% of the studies describing appropriate methods for both sequence generation and allocation concealment. Fifty per cent and 39% of the studies reporting benefit and harm outcomes, respectively, were subject to high risk. None of the studies included in the quantitative syntheses were judged to be at low risk of bias in all seven domains. The results described below pertain to the comparisons for daily risedronate 5 mg versus placebo which reported major outcomes. Other comparisons are described in the full text.

For primary prevention, low- to very low-certainty evidence was collected from four studies (one to two years in length) including 989 postmenopausal women at lower risk of fractures. Risedronate 5 mg/day may make little or no difference to wrist fractures [RR 0.48 ( 95% CI 0.03 to 7.50; two studies, 243 participants); absolute risk reduction (ARR) 0.6% fewer (95% CI 1% fewer to 7% more)] and withdrawals due to adverse events [RR 0.67 (95% CI 0.38 to 1.18; three studies, 748 participants); ARR 2% fewer (95% CI 5% fewer to 1% more)], based on low-certainty evidence. However, its preventive effects on non-vertebral fractures and serious adverse events are not known due to the very low-certainty evidence. There were zero clinical vertebral and hip fractures reported therefore the effects of risedronate for these outcomes are not estimable.

For secondary prevention, nine studies (one to three years in length) including 14,354 postmenopausal women at higher risk of fractures provided evidence. Risedronate 5 mg/day probably prevents non-vertebral fractures [RR 0.80 (95% CI 0.72 to 0.90; six studies, 12,173 participants); RRR 20% (95% CI 10% to 28%) and ARR 2% fewer (95% CI 1% fewer to 3% fewer), moderate certainty], and may reduce hip fractures [RR 0.73 (95% CI 0.56 to 0.94); RRR 27% (95% CI 6% to 44%) and ARR 1% fewer (95% CI 0.2% fewer to 1% fewer), low certainty]. Both of these effects are probably clinically important. However, risedronate's effects are not known for wrist fractures [RR 0.64 (95% CI 0.33 to 1.24); three studies,1746 participants); ARR 1% fewer (95% CI 2% fewer to 1% more), very-low certainty] and not estimable for clinical vertebral fractures due to zero events reported (low certainty). Risedronate results in little to no difference in withdrawals due to adverse events [RR 0.98 (95% CI 0.90 to 1.07; eight studies, 9529 participants); ARR 0.3% fewer (95% CI 2% fewer to 1% more); 16.9% in risedronate versus 17.2% in control, high certainty] and probably results in little to no difference in serious adverse events [RR 1.00 (95% CI 0.94 to 1.07; six studies, 9435 participants); ARR 0% fewer (95% CI 2% fewer to 2% more; 29.2% in both groups, moderate certainty).

**Authors' conclusions**

This update recaps the key findings from our previous review that, for secondary prevention, risedronate 5 mg/day probably prevents non-vertebral fracture, and may reduce the risk of hip fractures. We are uncertain on whether risedronate 5mg/day reduces clinical vertebral and wrist fractures. Compared to placebo, risedronate probably does not increase the risk of serious adverse events.

For primary prevention, the benefit and harms of risedronate were supported by limited evidence with high uncertainty.

## PLAIN LANGUAGE SUMMARY

**Risedronate for preventing fractures caused by osteoporosis in postmenopausal women**

This summary of a Cochrane Review presents what we know from the evidence up to 24 March 2021 about the effect of risedronate for preventing fractures (broken bones) caused by osteoporosis.

**What is osteoporosis and what is risedronate?**
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 the 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, like a little bump or fall. Women who have gone through menopause are more likely to get osteoporosis than other people.

Risedronate belongs to the class of drugs called bisphosphonates. It is a type of medication that slows down the cells that break down the old bone.

**In postmenopausal women whose bone density is closer to normal or who may not yet have had a fracture in the bones of their spine therefore putting them at lower risk for fractures:**

- there is insufficient evidence to tell us if risedronate leads to any reduction in the number of women sustaining bone fractures;

- based on limited data there is no evidence of an increase in adverse events for postmenopausal women at lower risk for fractures.

**In postmenopausal women who have already been diagnosed with osteoporosis (who have low bone density, or who have already had a fracture in the bones of their spine) putting them at higher risk for fractures, risedronate:**

- probably prevents fractures in the bones of the hip and in bones other than in the spine;

- may not lead to any difference in preventing wrist fractures;

- does not have enough evidence to show if it may prevent fractures in the bones of the spine suggested by clinical signs and symptoms;

- might make little or no difference in adverse events for postmenopausal women at higher risk for fractures.

**Best estimate of what happens to postmenopausal women at lower risk for fractures who take risedronate or placebo:**

- for spine fractures suggested by clinical signs and symptoms and hip fractures, it was not possible to calculate the effect because none of these fractures were reported in any of the studies;

- compared to placebo, there is not enough information to tell if risedronate prevents fractures in wrist and bones other than in the spine.

**Best estimate of what happens to postmenopausal women at higher risk for fractures who take risedronate or placebo:**

Fractures of the spine suggested by clinical signs and symptoms were not reported in any of the studies.

Fractures in bones other than the spine:

- 10 out of 100 women had a fracture when taking a placebo;

- 8 out of 100 women had a fracture when taking risedronate;

Fractures of the hip

- 3 out of 100 women had a fracture when taking a placebo;

- 2 out of 100 women had a fracture when taking risedronate.

Fractures of the wrist:

- there is not enough information to tell if risedronate prevents wrist fractures.

**Summary of findings 1. Risedronate 5 mg/day compared to placebo for the primary prevention of osteoporotic fractures in postmenopausal women**

**Risedronate 5 mg/day compared to placebo for the primary prevention of osteoporotic fractures in postmenopausal women**

**Patient or population:** postmenopausal women at lower risk of fractures[1]
**Setting:** outpatients
**Intervention:** risedronate 5 mg/day
**Comparison:** placebo

| Outcomes | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | | Certainty of the evidence (GRADE) | What happens |
|---|---|---|---|---|---|---|
| | | Without Risedronate 5 mg/day | With Risedronate 5 mg/day | Difference | | |
| Clinical vertebral fractures<br>assessed with: participant's clinical signs and symptoms<br>follow-up: 2 years<br>№ of participants: 170<br>(1 RCT) | not estimable | Study population | | | ⊕⊕⊖⊖<br>LOW [4] | Zero incidents were reported and the effect is not estimable. The effect of risedronate 5 mg/day on clinical vertebral fractures is unclear. |
| | | 0.0% | 0.0%<br>(0 to 0) | 0.0% fewer<br>(0 fewer to 0 fewer) | | |
| Non-vertebral fractures<br>assessed with: participant's clinical signs and symptoms<br>follow-up: range 1 year to 2 years<br>№ of participants: 497<br>(3 RCTs) | RR 0.54<br>(0.22 to 1.35) | Study population | | | ⊕⊖⊖⊖<br>VERY LOW [5, 6] | We do not know if risedronate 5 mg/day reduces non-vertebral fractures because the certainty of this evidence is very low. |
| | | 5.1% | 2.8%<br>(1.1 to 6.9) | 2.3% fewer<br>(4 fewer to 1.8 more) | | |
| | | Low | | | | |
| | | 8.6% [2] | 4.6%<br>(1.9 to 11.6) | 4.0% fewer<br>(6.7 fewer to 3 more) | | |
| | | Moderate | | | | |
| | | 16.5% [3] | 8.9%<br>(3.6 to 22.3) | 7.6% fewer<br>(12.9 fewer to 5.8 more) | | |
| Hip fractures | not estimable | Study population | | | ⊕⊕⊖⊖<br>LOW [4] | Zero incidents were reported therefore the effect is not es- |

| | | | | | | |
|---|---|---|---|---|---|---|
| assessed with: participant's clinical signs and symptoms<br>follow-up: range 1 year to 2 years<br>№ of participants: 243<br>(2 RCTs) | | 0.0% | 0.0%<br>(0 to 0) | 0.0% fewer<br>(0 fewer to 0 fewer) | | timable. The effect of risedronate 5 mg/day on hip fractures is unclear. |
| Wrist fractures<br>assessed with: adverse events reporting<br>follow-up: range 1 year to 2 years<br>№ of participants: 243<br>(2 RCTs) | RR 0.48<br>(0.03 to 7.50) | Study population | | | ⊕⊕⊖⊖<br>LOW [6] | Risedronate 5 mg/day may reduce wrist fractures. However, the 95% confidence interval indicates that risedronate might make little or no difference. |
| | | 1.1% | 0.5%<br>(0 to 8.2) | 0.6% fewer<br>(1.1 fewer to 7.1 more) | | |
| Withdrawals due to adverse events<br>assessed with: participant's clinical signs and symptoms<br>follow-up: range 1 year to 2 years<br>№ of participants: 748<br>(3 RCTs) | RR 0.67<br>(0.38 to 1.18) | Study population | | | ⊕⊕⊖⊖<br>LOW [6] | Risedronate 5 mg/day may reduce withdrawals due to adverse events. However, the 95% confidence interval indicates that risedronate might make little or no difference. |
| | | 7.4% | 5.0%<br>(2.8 to 8.8) | 2.4% fewer<br>(4.6 fewer to 1.3 more) | | |
| Serious adverse events<br>assessed with: participant's clinical signs and symptoms<br>follow-up: 2 years<br>№ of participants: 424<br>(2 RCTs) | RR 0.74<br>(0.42 to 1.30) | Study population | | | ⊕⊖⊖⊖<br>VERY LOW [5, 6, 7] | we do not know if risedronate 5 mg/day reduces serious adverse events because the certainty of this evidence is very low. |
| | | 13.9% | 10.3%<br>(5.8 to 18.1) | 3.6% fewer<br>(8.1 fewer to 4.2 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).

**CI:** Confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **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

[1] Postmenopausal women who did not fulfil any of the hierarchical criteria: a diagnosis of osteoporosis, a history of vertebral fractures, low bone mineral density T score < -2.5, or age ≥ 75 years old.
[2] 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).
[3] 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).

[4] Very few or zero events were reported in the included studies which had fewer than enough sample size to reach the optimal information. Downgraded two levels.
5 The overall effect was estimated from studies (or a study) rated as high risk of bias in the domain of incomplete outcome data (attrition bias). Downgraded one level.
[6] The optimal information size criteria was not met. There were few events and the confidence interval around both relative and absolute estimates of effect include both appreciable benefit and appreciable harm. Downgraded two levels (Schünemann 2013).
[7] Unexplained inconsistency, with point estimates widely different (P value Chi$^2$ = 0.07; I$^2$ e= 70%. Downgraded one level.

**Summary of findings 2. Risedronate 5 mg/day compared to placebo for the secondary prevention of osteoporotic fractures in postmenopausal women**

**,Risedronate 5 mg/day compared to placebo for the secondary prevention of osteoporotic fractures in postmenopausal women**

**Patient or population:**pPostmenopausal women at higher risk of fractures[1]
**Setting:** outpatients
**Intervention:** risedronate 5 mg/day
**Comparison:** placebo

| Outcomes | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | | Certainty of the evidence (GRADE) | What happens |
|---|---|---|---|---|---|---|
| | | Without Risedronate 5 mg/day | With Risedronate 5 mg/day | Difference | | |
| Clinical vertebral fractures<br>assessed with: participant's clinical signs and symptoms<br>follow-up: 1 years<br>№ of participants: 119<br>(2 RCTs) | not estimable | Study population | | | ⊕⊕⊖⊖<br>LOW [4] | Zero incidents were reported therefore the effect is not estimable. The effect of risedronate 5 mg/day on clinical vertebral fractures is unclear. |
| | | 0.0% | 0.0%<br>(0 to 0) | 0.0% fewer<br>(0 fewer to 0 fewer) | | |
| Non-vertebral fractures<br>assessed with: radiographic methods or participant's clinical signs and symptoms<br>follow-up: range 1 years to 3 years<br>№ of participants: 12,173<br>(6 RCTs) | RR 0.80<br>(0.72 to 0.90) | Study population | | | ⊕⊕⊕⊖<br>MODERATE [5, 6, 7] | Risedronate 5 mg/day probably reduces non-vertebral fractures and the reduction is probably clinically important. Relative risk reduction: 20% (95% CI 10% to 28%), NNTB: 50 (95% CI 35 to 98). |
| | | 10.2% | 8.2%<br>(7.4 to 9.2) | 2.0% fewer<br>(2.9 fewer to 1 fewer) | | |
| | | Moderate | | | | |
| | | 16.5% [2] | 13.2%<br>(11.9 to 14.9) | 3.3% fewer<br>(4.6 fewer to 1.6 fewer) | | |
| | | High | | | | |
| | | 27.5% [3] | 22.0% | 5.5% fewer | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (19.8 to 24.8) | (7.7 fewer to 2.7 fewer) | | |
| Hip fractures<br>assessed with: Radiographic methods or participant's clinical signs and symptoms<br>follow-up: range 1 years to 3 years<br>№ of participants: 9450<br>(3 RCTs) | RR 0.73<br>(0.56 to 0.94) | Study population | | | ⊕⊕⊖⊖<br>LOW [5, 8] | Risedronate 5 mg/day may reduce hip fractures and the reduction is probably clinically important. Relative risk reduction: 27% (95% CI 6% to 44%), NNTB: 127 (95% CI 76 to 560). |
| | | 3.0% | 2.2%<br>(1.7 to 2.8) | 0.8% fewer<br>(1.3 fewer to 0.2 fewer) | | |
| | | Moderate | | | | |
| | | 1.9% [2] | 1.4%<br>(1.1 to 1.8) | 0.5% fewer<br>(0.8 fewer to 0.1 fewer) | | |
| | | High | | | | |
| | | 8.7% [3] | 6.4%<br>(4.9 to 8.2) | 2.3% fewer<br>(3.8 fewer to 0.5 fewer) | | |
| Wrist fractures<br>assessed with: participant's clinical signs and symptoms<br>follow up: range 1 years to 3 years<br>№ of participants: 1746<br>(3 RCTs) | RR 0.64<br>(0.33 to 1.24) | Study population | | | ⊕⊖⊖⊖<br>VERY LOW [5, 9] | We don't know if risedronate 5 mg/day reduces wrist fractures because the certainty of this evidence is very low. |
| | | 2.5% | 1.6%<br>(0.8 to 3.1) | 0.9% fewer<br>(1.7 fewer to 0.6 more) | | |
| Withdrawals due to adverse events<br>assessed with: participant's clinical signs and symptoms<br>follow up: range 1 years to 3 years<br>№ of participants: 9529<br>(8 RCTs) | RR 0.98<br>(0.90 to 1.07) | Study population | | | ⊕⊕⊕⊕<br>HIGH [6, 10, 11] | Risedronate 5 mg/day may slightly reduce withdrawals due to adverse events. However, the 95% confidence interval indicates that risedronate might make little or no difference. |
| | | 17.2% | 16.9%<br>(15.5 to 18.4) | 0.3% fewer<br>(1.7 fewer to 1.2 more) | | |
| Serious adverse events<br>assessed with: participant's clinical signs and symptoms<br>follow-up: range 1 years to 3 years<br>№ of participants: 9435<br>(6 RCTs) | RR 1.00<br>(0.94 to 1.07) | Study population | | | ⊕⊕⊕⊖<br>MODERATE [5, 6, 11] | Risedronate 5 mg/day probably makes little or no difference to serious adverse events. |
| | | 29.2% | 29.2%<br>(27.4 to 31.2) | 0.0% fewer<br>(1.8 fewer to 2 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).

**CI:** Confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **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;tThe true effect is likely to be substantially different from the estimate of effect.

[1] Postmenopausal women who fulfilled at least one of the hierarchical criteria: a diagnosis of osteoporosis, a history of vertebral fractures, low bone mineral density T score < -2.5, and age ≥ 75 years old.
[2] 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).
[3] 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).
[4] Very few or zero events were reported in the included studies which had an insufficient sample size to reach the optimal information. Downgraded two levels.
[5] The overall effect was estimated from studies (or a study) rated as high risk of bias in the domain of incomplete outcome data (attrition bias). Downgraded one level.
[6] Evidence was estimated from studies (a study) judged to be at high risk in the domains of blinding of participants and personnel (performance bias) and outcome assessment (detection bias). However, the studies (study) carried very small weight and the impact was not considered serious. Not downgraded for ROB.
[7] In McClung 2001, patients assigned to risedronate group received daily doses of 2.5 or 5 mg. However, the sensitivity analysis excluding this study did not significantly change the magnitude and direction of the effect estimate for non-vertebral fractures. Not downgraded for indirectness.
[8] In McClung 2001, patients assigned to risedronate group received a daily dose of 2.5 or 5 mg. The results provided in this study may differ from the dose of interest (risedronate at 5 mg/day). Especially for hip fractures, McClung 2001 was the only study providing estimable data, so a sensitivity analysis excluding it was not feasible for testing the robustness of the results. Downgraded one level for indirectness.
[9] The optimal information size criteria was not met. There were few events and the confidence interval around both relative and absolute estimates of effect include both appreciable benefit and appreciable harm. Downgraded two levels.
[10] For withdrawals due to adverse events, all of the randomized participants were accounted for in most of the included studies. It was not downgraded for the high ROB in the domain of incomplete outcome data (attrition bias, safety outcome group).
[11] The optimal information size criteria was met. The 95% CI overlapped no effect and excluded important benefit (15%) (Schünemann 2013). Not downgraded for imprecision.

# BACKGROUND

## Description of the condition

Osteoporosis is in part a natural consequence of aging in postmenopausal women (Hodsman 2002). It is a skeletal disorder characterised by decreased bone mass and deterioration of 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 2002b). 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 2002b).

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 results is based on the comparison of a patient'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 2002b), for which the World Health Organization (WHO) Study Group recognises the following four diagnostic categories for women (WHO 1994).

1. Normal: a value for BMD or bone mineral content (BMC) within 1 SD of the young adult reference mean.
2. Low bone mass (osteopenia): a value for BMD or BMC more than 1 SD below the young adult mean but less than 2.5 SD below this value.
3. Osteoporosis: a value for BMD or BMC 2.5 SD or more below the young adult mean.
4. Severe osteoporosis (established osteoporosis): a value for BMD or BMC more than 2.5 SD 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 among women aged 50 years and older in nine industrialised 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 2014). In 27 countries of the European Union (EU27), 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 associated with the WHO definition. The predictive value of BMD measurement for fracture varies depending on the site selected, 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 regions of interest and different bone mass measurement techniques (Black 2001). The between-site and technique variability introduces 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 prior fracture after the age of 40 compared to those without had an increased risk of fracture (risk ratio (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 2002b). 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 2002b). Worldwide in the year 2000, it was estimated that 5.5 million women would experience fractures, among which hip was the second most prevalent 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). The mortality associated with hip fractures was observed to be high in the first year with a standardised mortality ratio (SMR) 1.9 (95% CI 1.2 to 2.7), which remained 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 9-fold, with the RR 8.64 (95% 4.45 to 16.74) (Cauley 2000). Although the mortality associated with non-hip non-vertebral fractures (NHNV) was likely to be lower compared to hip and vertebral fracture, the mortality impact of NHNV at the population level was studied in the CaMos cohort. The mortality risk for NHNV (followed up for a median time > 14 years) was found to be increased [hazard ratios (HR) 1.27, 95% CI 1.08 to 1.48)], but not to the same extent as that of hip (HR 2.14, 95% CI 1.62 to 2.84) and vertebrae (HR 1.93, 95% CI 1.42 to 2.64) (Tran 2017).

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 the baseline (Wainwright 2005). And in a sample of 482 women who had no previous knowledge of vertebral fracture, Greenspan 2001 also found that 36%, 34.6%, 30.7% and 30.7% of "non-osteoporotic women (osteopenia and normal BMD)" according to WHO classification criteria for spine BMD only, total hip only, femoral neck BMD only, and any central site BMD, respectively, had sustained a vertebral fracture. The prevention of fractures, therefore, is an important issue for postmenopausal women across 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 have 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. One class of anti-resorptive drugs includes the bisphosphonates, among which risedronate is recommended as one of the first-line treatment options for the majority of postmenopausal women (NOGG 2017),

or initial treatment for postmenopausal women at high risk of fractures (Eastell 2019). Since it became available in 2000, risedronate has been approved as a potent bisphosphonate to prevent fragility fractures (Wells 2008).

### How the intervention might work

Bisphosphonates are stable analogues of naturally occurring pyrophosphates, which inhibit bone resorption through their effects on osteoclasts (Brown 2002b). Bisphosphonates are poorly absorbed and avidly taken up by bone on active sites of resorption. Risedronate is a nitrogen-containing pyridinyl third generation bisphosphonate and the recommended doses for the prevention and treatment of osteoporosis in postmenopausal women are 5 mg/day, 35 mg/week or 150 mg/month (depending on formulation) . Risedronate at 5 mg, relative to control, has been shown to increase bone mineral density after 1.5 to three years of treatment by 4.54% (95% CI 4.12 to 4.97) in the lumbar spine, and 2.75% (95% CI 2.32 to 3.17) in the femoral neck (Cranney 2002). At a dose of 2.5 mg increases at the lumbar spine and femoral neck were 2.94% (95% CI 1.55 to 4.34) and 1.71%, (95% CI 1.17 to 2.25) (Cranney 2002).

### Why it is important to do this review

Risedronate is one of the oral bisphosphonates that have been widely prescribed (van der Velde 2017; Wysowski 2013). Different formulations have become available since it first came onto the market in 1998. An up-to-date review which includes all available trials comparing risedronate with both placebo and active drugs, and which incorporates evolving review methodologies (Higgins 2020; Higgins 2021) would be of benefit to current health care practice. To this end, we have integrated the following changes to our updated review.

1. A wider search including head-to-head comparisons and add-on studies of risedronate.
2. We did not exclude any study for not reporting fracture outcomes.
3. Peer-reviewed hierarchical criteria to differentiate evidence from studies including postmenopausal women at lower versus higher risk of fractures were developed and applied. A study was classified as secondary prevention if it recruited postmenopausal women who fulfilled more than one of the hierarchical criteria denoting a higher risk of fractures: a diagnosis of osteoporosis, a history of vertebral fractures, low bone mineral density T score ≤ -2.5, and/or age ≥ 75 years old. If the study included postmenopausal women who did not meet any of the above criteria, it was considered to be primary prevention (for women at lower risk of fractures).
4. Vertebral fractures were analysed separately as clinical or radiographic/morphometric vertebral fractures, since the two are not always synonymous. Greenspan 2001 found that 18.3 % of 482 asymptomatic (had no prior knowledge of vertebral fractures) postmenopausal women, had vertebral fractures determined by DXA. The Fracture Intervention Study (6084 women with available spinal radiographs) observed a discrepancy between vertebral fractures first identified through radiographic evidence versus patient' 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. Most of the clinical fractures on the other hand could be classified as severe, but 21.7% did not even meet the most liberal morphometric criterion (Fink 2005). In this review, we retained clinical vertebral fractures as a major outcome, but regarded radiographic vertebral fractures as a minor outcome.
5. Additional outcomes were included. Health-related quality of life was included to measure risedronate effects from patients' perspective. Gastrointestinal adverse events which have been linked to the use of oral bisphosphonate (Tadrous 2014) and accounted for a large proportion of adverse events and discontinuations in the previous version of this review (Wells 2008) were quantitatively analysed. Serious adverse events were added along with potential 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). 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 was investigated as well (Hewitt 2005).
6. In the base-case analysis, we used follow-up denominators (the number of patients assessed for that outcome) as our study numbers and conducted a sensitivity analysis using the baseline (the randomised) denominators.

## OBJECTIVES

To update the evidence and make it more clinically relevant, we assessed the benefits and harms of risedronate in the primary and secondary prevention of osteoporotic fractures.

## METHODS

### Criteria for considering studies for this review

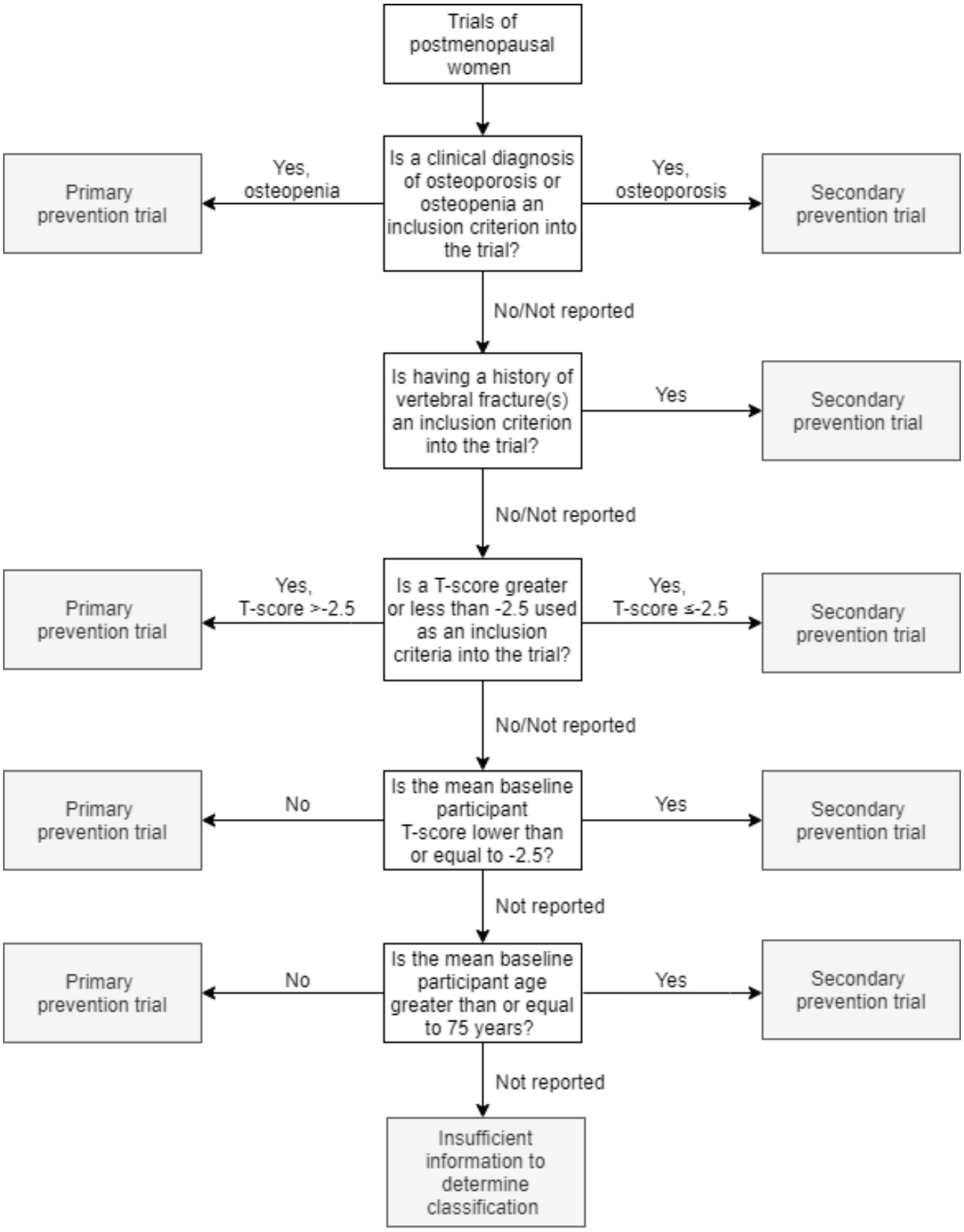
#### Types of studies

Randomised controlled trials (RCTs) with a duration of at least one year.

#### Types of participants

The population of interest included postmenopausal women with different risks of fracture. However, women with osteoporosis caused by underlying disease or medication were not included. 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. A hierarchy (Figure 1) was followed to classify trials as secondary prevention if the inclusion/exclusion criteria of the trial fulfilled one of the following criteria:

**Figure 1. Hierarchical Classification Algorithm for Primary and Secondary Prevention Trials**




1. participants diagnosed with osteoporosis;
2. participants were required to have a history vertebral fractures;
3. participant's bone mineral density (BMD) was required to be less than or equal to 2.5 standard deviations (SDs) of the bone

density in young healthy adults (peak bone mass). BMD T-score, at any measured site, e.g. lumbar spine, hip or others;

4. participant's mean baseline BMD T-score at any measured site was reported to be less than or equal to -2.5;
5. participants age was greater than or equal to 75 years old.

If none of the above criteria were met, the targeted study would be considered as a primary prevention trial. The hierarchical classification was peer-reviewed and deemed to reflect current clinical guidelines (AACE guidelines 2020; NOGG 2017; WHO 1994; WHO 2004) and practices. We planned to conduct a sensitivity analysis excluding studies defined by age, a criterion less than robust. In the event that studies were not definable by the hierarchical classification, narrative descriptions were provided.

### Types of interventions

Treatment: risedronate at any approved dosage/regimen, or risedronate combined with other anti-osteoporotic drugs. Eligible dosage regimens included daily 2.5 mg and 5 mg, weekly 17.5 mg and 35 mg, and monthly 150 mg given once or 75 mg in two consecutive days. All were for oral use.
Comparators: no treatment (including placebo or calcium or vitamin D or both), any anti-osteoporotic drugs alone or combined with risedronate were included. If the study used calcium or vitamin D controls or both, these same treatments would have to be given concurrently in the risedronate treatment group.

### Types of outcome measures

The following outcomes (if data were available) were considered in this review.

### Major outcomes

Fractures at the following anatomic sites were considered the most important, as well as two safety 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 fractures, 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 the base-case analysis, we extracted data at multiple time points (year) If data were available.

## Search methods for identification of studies

### Electronic searches

The electronic searches for this review were periodically updated in June 2012, August 2017, June 2019 and March 2021 (by the time this review was about to be accepted). For the update search in June 2012 when the review scope was expanded to include randomised active-controlled trials of risedronate, we consulted an Information Specialist, TR, in the Cochrane Musculoskeletal Group (CMSG) to broaden the search strategies, for which all the involved databases were searched from inception. In the following three updates, an experienced medical information specialist, BS, conducted the electronic searches with the same search strategies extended to 26 August 2017, 5 June 2019 and 24 March 2021. The following databases were all searched on the Ovid platform: Embase Classic + Embase, Ovid MEDLINE® (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations), and EBM Reviews - Cochrane Central Register of Controlled Trials. Search strategies used a combination of controlled vocabulary and keywords adjusted across databases with no restrictions placed on language or date and form of publication. The full search strategies from the 2012 and most updated (2021) search are in Appendix 1. Peer review of electronic search strategies (PRESS) 2015 guideline statement for systematic reviews was followed to achieve the comprehensiveness while maintaining acceptable precision for retrieved records (McGowan 2016).

No restrictions on language or date and form of publication were applied to any of the searches. We did not contact individual authors or organisations for further information to avoid bias.

### Searching other resources

Reference lists from all included studies and relevant systematic reviews and guidelines (Barrionuevo 2019; Chandran 2019; Ellis 2014; Hopkins 2011; Jansen 2011; Liu 2018; Migliore 2013; NOGG 2017; Taggart 2002; Yang 2016; Zhou 2016) were also scrutinised to identify any further relevant papers. 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 interventional studies involving risedronate. Studies retrieved from the clinical trial record databases were accessed at later dates for additional information. Drug approval documents and medical reviews developed by the United States Food and Drug Administration, European Medicines Agency, and Health Canada were initially searched for extractable information on 27 June 2019 (FDA Drug Approval Package-Actonel® 2000; Health Canada Product Monograph-Actonel® 2017).

## Data collection and analysis

### Selection of studies

Two review authors (SH and CZ) 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 (from SH, WL and CZ ) who independently abstracted data using standardised data abstraction forms developed in DistillerSR (Evidence Partners, Ottawa, Canada). Data accuracy was checked and discrepancies were resolved through discussion or, when required, by consulting a third review author (GW or JP). Review authors also collected and checked information on pertinent methodological aspects of the study design and characteristics of the participants.

Although included and data extracted, study arms using risedronate at doses and regimens not approved by any regulatory agency were not used in the analysis, i.e. cyclic risedronate 5 mg (risedronate daily for the first two weeks of every calendar month and placebo daily for the rest of the month) (Mortensen 1998) and intravenous ibandronate 0.5 mg/month (Nakamura 2013). Some formulations of risedronate which have been approved to have similar benefit and harm profiles in non-inferior clinical trials (Brown 2002; Delmas 2008a; Delmas 2008b; McClung 2012), and considered by drug regulatory authorities (FDA Drug Approval Package - Actonel®; Health Canada Product Monograph-Actonel®) as therapeutic equivalents for the treatment and prevention of postmenopausal osteoporosis, e.g. 5 mg/day, 35 mg/week, 150 mg/month, 75 mg/day for two consecutive days a month, were combined. When a study ended up with no pair-wise comparison after combining, it was not included in the analysis. The reported outcomes of interest were described separately and, if data were available, pooled for the comparisons between different therapeutically equivalent doses.

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 randomised participants. For health-related quality of life, we recorded the total number of randomised and follow-up participants, and the change from baseline if available. Fractures were extracted from the reports of new occurrences of fractures independently measured at different skeletal sites, e.g. vertebral, non-vertebral, hip and wrist, namely, the number of participant sustaining a fracture of interest. Vertebral fractures were defined as radiographic/morphometric or clinical events according to the method of assessment. For the former, there had to be a clear description of either radiographic or morphometric methods. However, if the event was reported as an adverse event without any outcome definition, it was classified as clinical vertebral fracture. In addition, all fracture outcomes were subject to subgroup analyses by treatment years so the yearly numbers of patients sustaining the fracture of interest among the follow-up participants were also collected. If the yearly follow-up 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, these were used for our analysis with the exception of outcomes for which the numerator was zero for pair-wise 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 fracture if the study reported zero fractures of any kind. Any inferred data were documented with reasons which were agreed upon and consistent through the data extraction.

The base case chosen for both primary and secondary prevention included the data available for the longest period of time (by year) for risedronate 2.5 mg/day or 5 mg/day in the placebo-controlled trial (that is, "all years"), and used the number of patients included in the respective outcome analysis as the denominator.

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

### Assessment of risk of bias in included studies

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

1. Adequacy of sequence generation: whether the method with which the study generated the allocation sequence is sufficient to produce comparable groups in every aspect except for the treatment.

2. Allocation concealment: whether the concealment method is sufficient to prevent detection 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 the knowledge of which intervention a participant was receiving. Blinding was assessed via domains 3 and 4.

3. performance bias for all outcomes: in clinical trials, to assure the effect estimates were a result of the intervention of interest and not other interventions (expected or unexpected), appropriate blinding methods to prevent participants and personnel from knowing the assigned treatment were required. Specifically in this review, the participants received anti-osteoporotic medications through different drug delivery routes and dose schedules for at least one year. Their compliance and relative health behaviours could be influenced if blinding was not maintained throughout the study. For study personnel, effective blinding could insure the provision of equal care and attention for all treatment groups.

4. detection bias was assessed separately for two outcome groups: objective and subjective. Objective outcomes included all fracture events which required clinical, radiographic, morphometric evidence to make a diagnosis so were less likely to be influenced by the lack of or inappropriate blinding. Subjective outcomes included adverse events and health-related quality of life for which the lack of or inappropriate blinding could influence the participants' or assessors' knowledge of the allocated interventions.

5. Incomplete outcome data: we separated the assessment for attrition bias into two outcome groups, efficacy and safety. 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 randomised, reasons for the attrition/exclusions and approaches to handling missing data. We arbitrarily took the overall completion rate of 80% as a cut-off for low risk of bias. If it was close to 80%, two more factors were considered: a) whether 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).

6. Selective reporting bias: in addition to the literature search, we searched C*linicalTrial.gov* and World Health Organization International Trials Registry Platform for protocols of included studies. If the study protocol was available, the pre-specified outcomes were compared with the reported outcomes in the published study with respect to individual outcomes and primary/secondary endpoints. However, for those studies without accessible protocols, the pre-defined outcomes of interest in the 'methods section' of the published study were checked against those reported in the 'results section' of the published study.

7. Other sources of bias: we assessed any concern outside of 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).

Each domain was depicted in two parts. The first part described what happened in the study, and the second part provided the judgment indicating a "low" , "high", or "unclear" (when there was insufficient information) risk. Any disagreements were resolved through discussion among the review authors until consensus was reached, or by adjudication with a third review author. In cases where the outcome (group) was not addressed or outcome data were not extractable or not comparable, the assessment was rated as "unclear" (Higgins 2017).

### 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, wrist and radiographic vertebral fractures, withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, atypical femoral fractures, acute phase reaction, osteonecrosis of the jaw, and atrial fibrillation. For the continuous outcome, health-related quality of life, we used mean differences (MD) between the two groups' change from baseline. To accommodate different measurement scales, standardised mean differences (SMDs) were used (Deeks 2019). 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.

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 patients sustaining the outcome among the number of participants followed up (denominators). Outcomes reported as number of events were not usable unless there was only 0 or one event, in which case 0 or one participant could be inferred.

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

For all studies, we also considered the longest follow-up with available data (by year) as the base-case analysis. Pair-wise comparisons extracted from studies comparing more than 2 intervention groups were scrutinized to avoid double-counting of participants in the same meta-analysis (Deeks 2019).

### 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 the end-of-study denominator was not available, we used the baseline denominator instead. When data were only available in graphic format, we plotted numbers/percentages of the events from figures with the web-based tool, WebPlotDigitizer-4.1 (Rohatgi 2018). Where extracted data were inferred, plotted or calculated, the relevant source and the reviewer's reasoning were also documented.

### Assessment of heterogeneity

When a meta-analysis was feasible, the results were presented in forest plots, and the $I^2$ statistic was used to measure the percentage of variability in treatment effects due to between-study heterogeneity rather than chance. An $I^2$ greater than 50% indicating substantial or considerable heterogeneity was qualitatively investigated in terms of clinical and methodological differences across studies. We also tested for homogeneity using a $Chi^2$ test with a cut-off of P = 0.10 for presence of statistical heterogeneity (Deeks 2019).

### Assessment of reporting biases

We made efforts to link relevant references to the included studies and to avoid multiple uses of the data. The companion publications providing additional outcome data were listed under the main reference; while those without additional outcome data were excluded with the reason "Companion record to included study but with no additional outcome".

To assess reporting bias, we planned to test the funnel plot asymmetry when there were more than 10 included studies available for meta-analysis of a specific outcome.

No restrictions were placed 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 risk ratio (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 2008) 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 2019). However, an investigation of the extent of heterogeneity was provided with a non-significant test (P value >0.10) (Deeks 2019). 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 cChi$^2$ test procedure taking a P value < 0.05 for presence of statistical association. For continuous outcomes, (e.g. health-related quality of life), measures were converted to a standardised mean difference(SMD) and a pooled estimate was provided 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 risedronate compared with the comparator was considered. Whenever a meta-analysis was not possible, we provided a descriptive summary.

For the base case of the placebo-controlled trials, we followed our original review and defined a >15% relative change with precision as being clinically important (Wells 2008). For any important benefit, we planned to calculate and present the absolute risk reduction (ARR) and number needed to treat for an additional beneficial outcome (NNTB) 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) from Black 2001 (Appendix 2; Appendix 3), and the lifetime and five-year age-specific risks in the untreated population were based on the model by Doherty 2001 (Appendix 4) for predicting osteoporotic fractures in postmenopausal women.

### Subgroup analysis and investigation of heterogeneity

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

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

### Sensitivity analysis

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

1) Analysis including all randomised participants (baseline) in the 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 randomised trials (Newell 1992), it would likely under-estimate the incidents of adverse health outcomes, such as fractures. This bias could affect the trials where the end-of-study data were extracted based on a smaller population than the total number randomised (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.

2) Studies with fracture as an efficacy outcome. Ideally, evaluating fractures as efficacy outcomes would result in better operational fracture definitions, more thorough statistical methods, and an attempt to 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 potentially provide anti-fracture estimates closer to the truth. This assumption, nevertheless, needs further investigation.

3) Studies of high-methodological quality, defined as full publication of peer-reviewed randomised studies (i.e. not conference abstracts) with low risk of bias for allocation concealment (i.e. reported clearly the methods that were used to conceal participant allocation) and incomplete (efficacy) outcome data (i.e. end-of-treatment follow-up rate of at least 80% or close to 80% with balanced attrition numbers and reasons across treatment arms). It was assumed that the results from studies with high-methodological quality would be closer to the truth.

4) Analysis excluding primary/secondary prevention studies classified on age alone.

5) Excluding McClung 2001 from the base-case analysis. In this study, patients were assigned to receive placebo or risedronate 2.5 mg/day or 5 mg/day. The reported outcome data for the risedronate arm combinedtwo2 doses. By including this study in the 5 mg base case, there was uncertainty regarding the anti-fracture effect estimates of risedronate 5 mg/day on its own. A sensitivity analysis excluding this study was therefore conducted.

### Summary of findings and assessment of the certainty of the evidence

We constructed two summary of findings tables using the GRADE approach (GRADE 2015; Schünemann 2013) to provide recommendations incorporating relevance, applicability and certainty of evidence from this review. The base-case results for risedronate 5 mg/day compared with placebo for primary and secondary prevention were used. Four fracture outcomes, including clinical vertebral, non-vertebral, hip, and wrist fractures (benefits) and two harms, including withdrawals due to adverse events and serious adverse events, were considered clinically important and included in the summary of findings tables. Following GRADE, the outcome evidence was assessed for factors that could reduce its certainty, i.e. study limitations (ROB), inconsistency of results, indirectness of evidence, imprecision, and publication bias.

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 women were at lower risk of fractures, assumed low- and moderate-fractures risks were derived from the quintiles of FRACTURE index 1-2 and FRACTURE index 5, respectively. For secondary prevention where the included women were at higher risk of fractures, assumed moderate to high fractures risks were derived from the quintiles of FRACTURE index

5 and FRACTURE index 8-13, respectively (Appendix 3). Where the data were available, the anticipated absolute effects were shown for each clinical scenario.

# RESULTS

## Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

### Results of the search

The initial search of the databases identified 2088 records. We also found 514 records by searching grey literature. After removing duplicates, 2051 records were screened and 1881 were excluded as their titles or abstracts did not meet the inclusion criteria. One hundred and seventy full-text articles or abstracts were examined further. Of these, 43 unique studies (and 14 companion publications) were included for qualitative synthesis, 11 studies not reporting any outcome of interest were listed as awaiting classification (Benhamou 2013; Bilek 2016; Felsenberg 2010; Ia Vilariño 2009; Lim 2019; Matsuzaki 2012; Okamoto 2010; Pastore 2014; Seeman 2010; Yeter 2014; Yildirim 2005), and 102 studies were excluded with reasons provided.

Nine publications were identified from the updated literature search conducted on 24 March 2021, including one companion article (Body 2020), which reported clinical vertebral fracture for Kendler 2018, one new study reporting data for non-vertebral fractures, withdrawals due to adverse events and serious adverse events (NCT00386360), and two reporting outcomes of interest for which data were not extractable (Deng 2020; Hagino 2014). The addition of these data does not substantially change the direction or magnitude to the results, therefore, we have listed them as studies awaiting classification in addition to five registered protocols (NCT00345644; NCT00402441; NCT00790101; NCT01904110; UMIN000010017) which did not post any results.

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

**Figure 2. PRISMA Diagram** * **In the literature update search conducted on 24 March 2021, eight new studies (one reporting and seven not reporting outcome data) and one companion article were identified.**

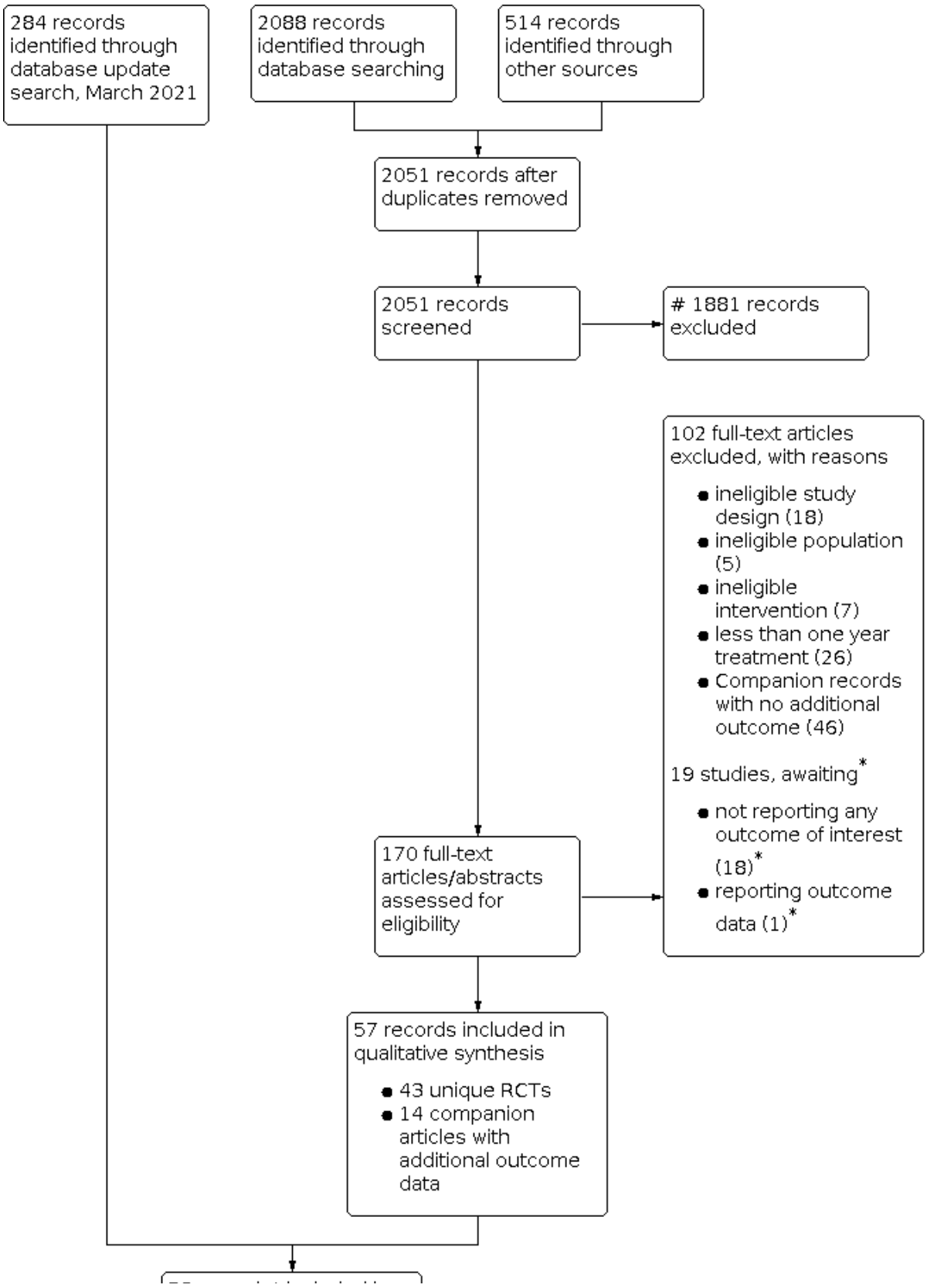
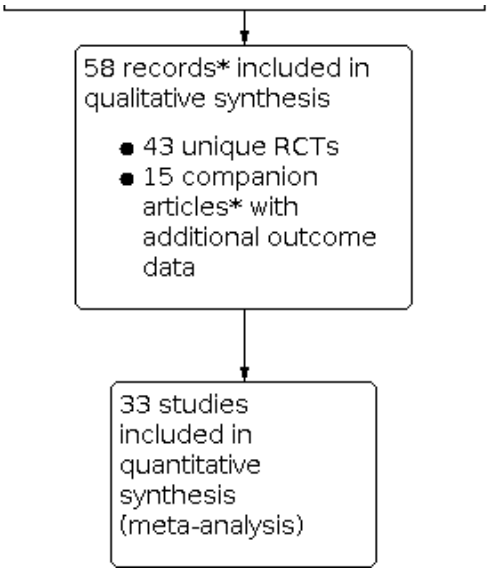


**Figure 2. (Continued)**




### Included studies

The 43 eligible studies were parallel randomised trials and reported at least one outcome of interest. Details and the risk of bias assessments are provided in the 'Characteristics of included studies' table. In this updated review, 36 more studies were included.

According to the hierarchical classification, there were nine primary (Bala 2014; Harris 2001; Hooper 2005; Kato 2010; Gu 2015; Mortensen 1998; Muscoso 2004; Rosen 2005; Välimäki 2007) and 33 secondary prevention trials (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Brown 2002; Clemmesen 1997; Delmas 2008a; Delmas 2008b; Dobnig 2006; Dundar 2009; Fogelman 2000; Fukunaga 2002; Galesanu 2011; Hadji 2012; Harris 1999; Hosking 2003; Kasukawa 2014; Kendler 2018; Leung 2005; Li 2005; McClung 2001; McClung 2012; Nakamura 2013; Narula 2012; NCT00365456; NCT02063854; Ohtori 2013; Paggiosi 2014a; Reginster 2000; Reid 2006; Roux 2014; Sarioglu 2006; Tanaka 2017; Yanik 2008). In addition, one study was undefined (Lim 2017) due to insufficient information. Table 1 summarises the criteria used to classify the included studies into primary and secondary prevention populations. Most studies met more than one classification criteria.

Ten of the 43 eligible studies which were not included in the main quantitative syntheses were either narratively described, or analysed separately and summarised. Table 1, Appendix 5 describes four studies whose data were not extractable, including three newly included (Kato 2010; Lim 2017; Narula 2012) and one (Clemmesen 1997) included in the original review. Among these, one was defined as primary prevention (Kato 2010), two as secondary prevention (Clemmesen 1997; Narula 2012), and one was undefined (Lim 2017). Five studies comparing different approved dose regimens of risedronate were analysed separately (Analysis 29.5 to Analysis 29.12) and summarised in Table 2, Appendix 5 (Brown 2002; Delmas 2008a; Delmas 2008b; Gu 2015; McClung 2012). The comparisons included one primary prevention study comparing risedronate 5 mg/day and 35 mg/week (Gu 2015), and two, one and one secondary prevention trials which compared risedronate 5 mg/day with its therapeutic equivalents of 35 mg/week (Brown 2002; McClung 2012), 150 mg/month (Delmas 2008a) and 75 mg/day for two consecutive days a month (Delmas 2008b), respectively. For the comparisons for risedronate at approved versus unapproved dose regimens, three studies were analysed (Brown 2002; Mortensen 1998; NCT02063854) and the results are summarised in Table 3, Appendix 5.

The remaining 33 studies included in the quantitative analyses were all randomised controlled trials (RCTs) published between 1998 and 2017. Studies were conducted in more than one country in 13 RCTs. Nineteen studies were conducted in a single country, including China (two studies), Japan (five studies), Turkey (four studies), and one each in Australia, Denmark, Germany, Greece, Italy, Romania, the UK and the USA. Twenty-two studies reported their sources of funding, among which one was not funded, one was funded by not-for-profit organisations, and 20 were founded by industry. Twenty-one (64%), 11 (33%), and one (3%) were 2-arm, 3-arm, and 4-arm trials, respectively. In total, 27,348 participants were included in seven primary studies (4566 women) (Bala 2014; Harris 1999; Hooper 2005; Mortensen 1998; Muscoso 2004; Rosen 2005; Välimäki 2007) and 26 secondary prevention studies (22,782 women) (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Dobnig 2006; Dundar 2009; Fogelman 2000; Fukunaga 2002; Galesanu 2011; Hadji 2012; Harris 1999; Hosking 2003; Kasukawa 2014; Kendler 2018; Leung 2005; Li 2005; McClung 2001; Nakamura 2013; NCT00365456; Ohtori 2013; Paggiosi 2014a; Reginster 2000; Reid 2006; Roux 2014; Sarioglu 2006; Tanaka 2017; Yanik 2008).

There were differences in study characteristics between primary and secondary prevention trials. Seven primary prevention studies were published between 1998 and 2014 with study periods ranging from one to two years. Four were placebo-controlled trials of daily risedronate (mainly 5 mg) recruiting 989 participants (Bala 2014; Hooper 2005; Mortensen 1998; Välimäki 2007). Of the three active controlled studies: Rosen 2005 compared weekly use of risedronate (35 mg) with alendronate (70 mg) in 1053 participants. Harris 2001 investigated the additional effects of risedronate (5 mg/day) to hormone replacement therapy (HRT,

oral oestrogen 0.625 mg/day) in 524 participants. Muscoso 2004 recruited 2000 participants and compared daily risedronate (5 mg) with three anti-resorptive drugs, including alendronate (10 mg/day), intramuscular clodronate (100 mg/week) and raloxifene (60 mg/day). One study prohibited background supplementation (Mortensen 1998), while the remaining five studies included daily use of calcium 1000 mg and vitamin D 400 IU to 800 IU during the study period (Harris 2001; Hooper 2005; Muscoso 2004; Rosen 2005; Välimäki 2007).

Twenty-six secondary prevention studies were published between 1999 and 2017, with 81% (21 studies) of them post 2005. Study periods ranged from one to four years. Ten were placebo-controlled trials (Dobnig 2006; Dundar 2009; Fogelman 2000; Harris 1999; Hosking 2003; Leung 2005; Li 2005; McClung 2001; Ohtori 2013; Reginster 2000), and 18 provided at least one active treatment comparison (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Fukunaga 2002; Galesanu 2011; Hadji 2012; Hosking 2003; Kasukawa 2014; Kendler 2018; Nakamura 2013; NCT00365456; Ohtori 2013; Paggiosi 2014a; Reid 2006; Roux 2014; Sarioglu 2006; Tanaka 2017; Yanik 2008). For the former, risedronate 5 mg/day was most frequently investigated (eight studies), followed by 2.5 mg/day (five studies) and 35 mg/week (one study). Two placebo-controlled trials also included an active arm: one compared risedronate 5 mg/day with alendronate 70 mg/week (Hosking 2003), and another compared risedronate 2.5 mg/day with daily subcutaneous injection of teriparatide 20 µg (Ohtori 2013). Among all pair-wise active comparisons of risedronate, weekly use (35 mg) was most frequently studied (nine studies). The active comparators included alendronate 70 mg/week (seven studies) and 10 mg/day (one study), subcutaneous injection of teriparatide 20 µg/day (four studies), oral ibandronate 150 mg/month (two studies), and one each of etidronate 200 mg/day, intravenous injection of ibandronate 1 mg/month, raloxifene 60 mg/day, subcutaneous injection of denosumab 60 mg/6 months and parathyroid hormone (PTH 1-84) 100 IU/day. The combined use of risedronate with another anti-osteoporotic drug was investigated in two studies, both of which looked at the additional effects of menatetrenone (Vitamin $K_2$) combined with risedronate 2.5 mg/day or 17.5 mg/week (Kasukawa 2014; Tanaka 2017). Randomized study populations ranged from 30 to 9331 and totaled 22,782. Eight RCTs randomised 100 or fewer participants, while six RCTs randomised 1000 or more participants (Harris 1999; Kendler 2018; McClung 2001; Nakamura 2013; Reginster 2000; Tanaka 2017). Twenty-three studies reported the daily use of calcium (200 mg to 1200 mg) with or without vitamin D (≦ 800 IU) (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Bala 2014; Dobnig 2006; Dundar 2009; Fogelman 2000; Fukunaga 2002; Hadji 2012; Harris 1999; Hosking 2003; Kendler 2018; Leung 2005; Li 2005; McClung 2001; Nakamura 2013; Paggiosi 2014a; Reginster 2000; Reid 2006; Roux 2014; Sarioglu 2006; Tanaka 2017; Yanik 2008), while three studies prohibited any background supplementation (Galesanu 2011; Kasukawa 2014; Ohtori 2013).

As expected, participants (4566 included) in primary prevention studies had fewer (or milder) risk factors than those in the secondary (22,782 included) prevention trials, including age (primary: 51.5 to 68.0 years old versus secondary: 56.7 to 77.7 years old), time since menopause (primary: 2.7 to 18.5 years vs secondary: 12.9 to 31.7 years), body mass index (BMI) (primary: 23.0 versus 25.4 versus secondary: 21.4 to 32.7), BMD T-score at femoral neck (primary: 0.76 to -2.14 vs secondary: -1.44 to -3.70) or at lumbar spine (primary: -0.4 to -2.25 vs secondary: -2.20 to -3.62) and prevalent vertebral fractures (primary: 0% to 28% versus secondary: 10% to 100%). Regarding prior osteoporotic treatment, two primary prevention studies (Bala 2014; Hooper 2005) and five secondary prevention studies (Akyol 2006; Dundar 2009; Kasukawa 2014; Li 2005; Reginster 2000) included only bisphosphonate-naïve participants; and two secondary prevention studies (NCT00365456; Roux 2014) included only participants who had previous exposure to any bisphosphonate. In addition, four out of six primary prevention studies reporting participant's ethnicity predominantly recruited Caucasians (> 95%) (Hooper 2005; Mortensen 1998; Rosen 2005; Välimäki 2007). Although the most frequently reported ethnicity in the secondary prevention studies was Caucasian (79% to 100%), five studies conducted in Japan (Fukunaga 2002; Kasukawa 2014; Nakamura 2013; Ohtori 2013; Tanaka 2017) and two in China (Leung 2005; Li 2005), were likely to include only Asian participants.

### Excluded studies

A total of 102 articles were excluded for various reasons, including ineligible study design (18 studies) (Article in Dutch 2001,Brown 2014; Duque 2009; Eastell 2010; Goa 1998; Hosking 2009; Kendler 2009; Licata 1997; Maugeri 2005; Recker 2015; Reginster 2001; Reszka 1999; Roux 2004; Seibel 2004; Singer 1995; Stovall 2010; Sunyecz 2009; Watts 1998), ineligible population (five studies) (Carlino 2011; Fujita 2009; Kushida 2004; Miller 1999a; Palomba 2005), ineligible intervention/comparators (seven studies) (Caffarelli 2010; Delmas 2007; Eastell 2011; Gonnelli 2006; Iizuka 2008; Ralston 2011; Watts 2008), treatment period less than one year (26 studies) (Adachi 2001; Altintas 2007; Anastasilakis 2008b; Bahlous 2009; Chung 2009; D'Amelio 2008; Dane 2008; Gossiel 2010; Hongo 2015; Ilter 2006; Iwamoto 2016; Karadag-Saygi 2011; Lanza 2000; Lanza 2000a; Ohtori 2012; Oktem 2008; Oliveira 2015; Oral 2015; Pawlowski 2015; Peris 2013; Racewicz 2007; Shiraki 2003; Ste-Marie 2009; Takada 2007; Thomson 2002; Zegels 2001), and companion publication to included studies with no additional outcome data (46 studies) (Bala 2013; Borah 2004; Borah 2005; Borah 2010; Borah 2010a; Chapurlat 2011; Dufresne 2003; Duque 2011; Durchschlag 2006; Eastell 2003; Eastell 2013; Eriksen 2002; Geusens 2017; Gossiel 2016; Gossiel 2018; Hadji 2011; Hadji 2011a; Hagino 2014; Harris 1999a; Hofbauer 2013; Hooper 1999; Imai 2017; Kanis 2005; Kendler 2017; Masud 2009; McClung 1996; McClung 1998; McClung 2010a; McClung 2010b; McClung 2010c; McClung 2011; Mellstrom 2004; Miller 1999; Minisola 2019; Paggiosi 2014b; Recker 2011; Ribot 1999; Roux 2013; Sebba 2004; Seeman 2010a; Tanaka 2014; Taquet 1996; Watts 1999; Watts 2003; Zerbini 2017; Zoehrer 2006).

## Risk of bias in included studies

Forty-three eligible studies were assessed for risk of bias (ROB), including the 10 which did not provide any outcome data for analysis (Characteristics of included studies). Figure 3 provides a graphical summary of risk of bias for all of the included studies. None of the studies were at low risk of bias for all eight domains. Figure 4 summaries 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' judgements about each risk of bias item for each included study.**

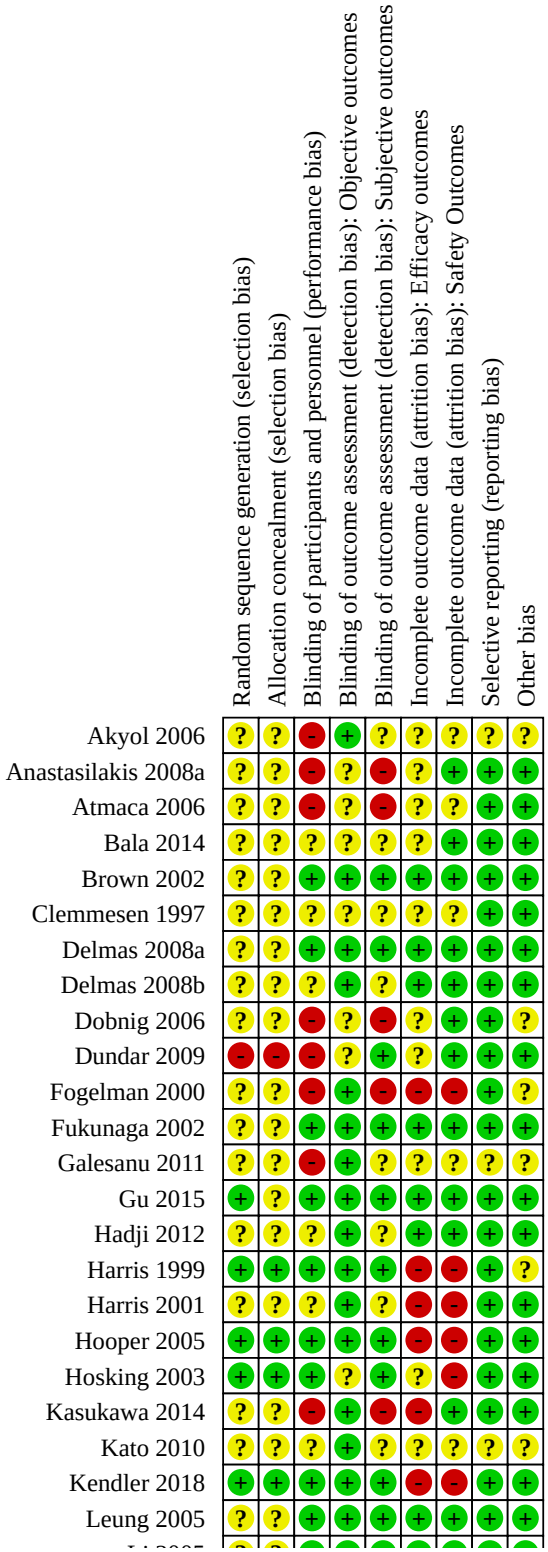


**Figure 3. (Continued)**

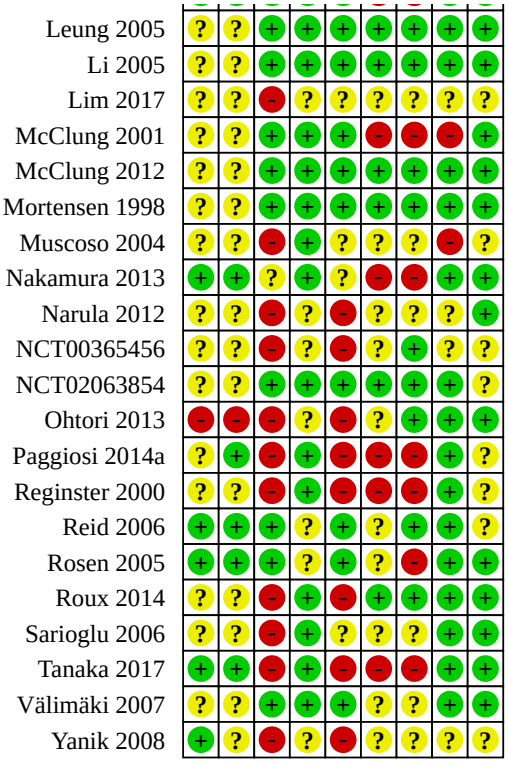
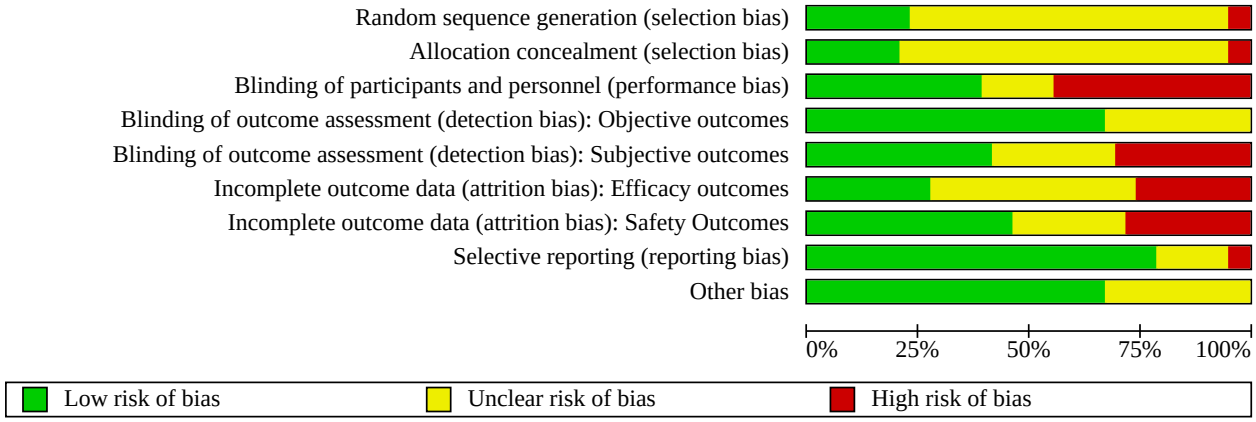



**Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**




For the following discussions about the ROB results, however, we only included the 33 studies included in the quantitative analyses (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Bala 2014; Dobnig 2006; Dundar 2009; Fogelman 2000; Fukunaga 2002; Galesanu 2011; Hadji 2012; Harris 1999; Harris 2001; Hooper 2005; Hosking 2003; Kasukawa 2014; Kendler 2018; Leung 2005; Li 2005; McClung 2001; Mortensen 1998; Muscoso 2004; NCT00365456; Nakamura 2013; Ohtori 2013; Paggiosi 2014a; Reginster 2000; Reid 2006; Rosen 2005; Roux 2014; Sarioglu 2006; Tanaka 2017; Välimäki 2007; Yanik 2008).

### Allocation

#### *Sequence generation*

Only ten out of 33 studies clearly described the methods for sequence generation that were judged to be appropriate, including the use of a computerised randomisation schedule (Gu 2015; Harris 1999; Hooper 2005; Hosking 2003; Kendler 2018; Reid 2006; Rosen 2005; Tanaka 2017), minimisation (Nakamura 2013) or random numbers table (Yanik 2008). Two studies claimed that randomisation was conducted but the methods of assignment were

not appropriate. Dundar 2009 assigned every first and second person to the treatment group and every third person to the control group, following a list of names ordered according to time and date of recruitment. Ohtori 2013 assigned participants to three groups and then allocated all participants of the first, second and third group to control, risedronate and teriparatide group, respectively. The generation of the sequence in both studies were not at random so were judged to be at high risk of bias. The remaining 22 studies used descriptors such as "randomised", "randomly assigned" or "randomly divided" but did not provide sufficient information for judgment.

#### *Allocation concealment*

Nine studies, either applying interactive voice response system (Kendler 2018; Nakamura 2013) or confirming that the randomisation schedule was held by a central (third) party and/or that the treatment allocation remained unknown to the patients and research personnel (Hooper 2005; Hosking 2003; Kendler 2018; Paggiosi 2014a; Reid 2006; Rosen 2005; Tanaka 2017), were judged to be at low risk of bias. In Dundar 2009 and Ohtori 2013, however, as described in the previous domain, the investigators and participants would have easily guessed the assigned treatment, so were judged to be at high risk of bias regardless of any concealment method in place. The remaining 23 studies which did not provide any method for allocation concealment were judged to be of unclear risk of bias.

When we look at the combined domains of sequence generation and allocation concealment for selection bias, eight studies (Harris 1999; Hooper 2005; Hosking 2003; Kendler 2018; Nakamura 2013; Reid 2006; Rosen 2005; Tanaka 2017) were judged to be at low risk.

### Blinding

#### *Performance bias (all outcomes)*

Twelve studies were double-blinded using methods that were judged appropriate (Fukunaga 2002; Harris 1999; Hooper 2005; Hosking 2003; Kendler 2018; Leung 2005; Li 2005; McClung 2001; Mortensen 1998; Reid 2006; Rosen 2005; Välimäki 2007). Another four studies claimed to be double-blinded, but they did not provide methods or sufficient information for judgment (Bala 2014; Hadji 2012; Harris 2001; Nakamura 2013). Among the remaining 17 judged to be at high risk of bias, six were described by the authors as "open-label" (Anastasilakis 2008a; Dobnig 2006; NCT00365456; Ohtori 2013; Paggiosi 2014a; Roux 2014), and nine were suspected to be open-label given that the treatments were notably different so the blinding was either not feasible or could easily be broken (Akyol 2006; Atmaca 2006; Dundar 2009; Galesanu 2011; Kasukawa 2014; Muscoso 2004; Sarioglu 2006; Tanaka 2017; Yanik 2008). In addition, Fogelman 2000 and Reginster 2000, although reported to be double-blind, did not provide the blinding approach at all. Due to the early discontinuation of 2.5 mg arm which might have impacted the maintenance of the blinding, they were judged to be at high rather than unclear risk of bias.

#### *Detection bias (objective outcomes)*

For objective outcomes, 22 studies (Akyol 2006; Fogelman 2000; Fukunaga 2002; Galesanu 2011; Hadji 2012; Harris 1999; Harris 2001; Hooper 2005; Kasukawa 2014; Kendler 2018; Leung 2005; Li 2005; McClung 2001; Mortensen 1998; Muscoso 2004; Nakamura 2013; Paggiosi 2014a; Reginster 2000; Roux 2014; Sarioglu 2006; Tanaka 2017; Välimäki 2007) reporting fracture data for analyses were judged to be at low risk of bias regardless of the blinding methods used. For the remaining 11 studies which did not report any usable fracture data, assessment was judged as unclear risk of bias (Anastasilakis 2008a; Atmaca 2006; Bala 2014; Dobnig 2006; Dundar 2009; Hosking 2003; NCT00365456; Ohtori 2013; Reid 2006; Rosen 2005; Yanik 2008).

#### *Detection bias (subjective outcomes)*

Twelve studies (Fukunaga 2002; Harris 1999; Hooper 2005; Hosking 2003; Kendler 2018; Leung 2005; Li 2005; McClung 2001; Mortensen 1998; Reid 2006; Rosen 2005; Välimäki 2007) either describing the use of "matching placebo" or emphasising that the placebo was identical (indistinguishable) to the active drug in terms of the smell, taste and shape were judged appropriate to maintain the blinding throughout the study. In Dundar 2009, although suspected as open-label, withdrawals due to adverse events was the only subjective outcome reported and no incident occurred, so it was judged to be at low risk of bias. Twelve studies were judged to be at high risk of bias (Anastasilakis 2008a; Atmaca 2006; Dobnig 2006; Fogelman 2000; Kasukawa 2014; NCT00365456; Ohtori 2013; Paggiosi 2014a; Reginster 2000; Roux 2014; Tanaka 2017; Yanik 2008). Four studies which claimed to be "double blind" but did not describe the blinding methods used (Bala 2014; Hadji 2012; Harris 2001; Nakamura 2013) were judged as unclear risk of bias, in addition to four studies (Akyol 2006; Galesanu 2011; Muscoso 2004; Sarioglu 2006) which did not report any usable safety outcome data.

### Incomplete outcome data

#### *Attrition bias (efficacy outcomes)*

For efficacy outcomes, the bias from incomplete outcome data were judged to be at low risk for five studies (Fukunaga 2002; Leung 2005; Li 2005; Mortensen 1998; Roux 2014). They had adequate completion rates (ranging from 85% to 95%) with balanced withdrawals and reasons for early discontinuations across groups. Additionally, Hadji 2012 reporting balanced numbers and reasons of the early discontinuations across groups was judged to be at low risk of bias although the completion rate was 74%. Five studies, however, were judged to be at unclear risk of bias in this domain (Akyol 2006; Galesanu 2011; Muscoso 2004; Sarioglu 2006; Välimäki 2007) for not providing any information about the statistical methods and attrition. For 11 studies which did not report any efficacy outcomes (Anastasilakis 2008a; Atmaca 2006; Bala 2014; Dobnig 2006; Dundar 2009; Hosking 2003; NCT00365456; Ohtori 2013; Reid 2006; Rosen 2005; Yanik 2008) assessment for this domain was not applicable. Eleven studies which had comparatively low overall completion rates or unclear reporting of attrition across groups were judged to be at high risk of bias (Fogelman 2000; Harris 1999; Harris 2001; Hooper 2005; Kasukawa 2014; Kendler 2018; McClung 2001; Nakamura 2013; Paggiosi 2014a; Reginster 2000; Tanaka 2017). In addition, for Fogelman 2000, Harris 1999 and Reginster 2000, the 2.5 mg/day risedronate arm was discontinued early due to protocol amendment, thus both the reported efficacy and safety outcomes data for this dose were further subject to bias.

#### *Attrition bias (safety outcomes)*

Thirteen studies were judged to be at low risk of bias (Anastasilakis 2008a; Bala 2014; Dobnig 2006; Dundar 2009; Fukunaga 2002; Hadji

2012; Leung 2005; Li 2005; Mortensen 1998; NCT00365456; Ohtori 2013; Reid 2006; Roux 2014). In addition, Kasukawa 2014 which had a < 80% completion rate, reported only one safety outcome (withdrawals due to adverse events) which included all randomised participants and was therefore considered to be less biased by high attrition. Twelve studies reporting safety outcomes were judged to be at high risk of bias given high attrition and/or unbalanced discontinuations across groups (Fogelman 2000; Harris 1999; Harris 2001; Hooper 2005; Hosking 2003; Kendler 2018; McClung 2001; Nakamura 2013; Paggiosi 2014a; Reginster 2000; Rosen 2005; Tanaka 2017). Five studies provided limited information to allow for assessment (Atmaca 2006; Galesanu 2011; Sarioglu 2006; Välimäki 2007; Yanik 2008), in addition to two studies (Akyol 2006; Muscoso 2004) which did not report any safety outcome, were judged to be at unclear risk of bias

#### Selective reporting

All but six included studies reporting at least one outcome of interest were judged to be at low risk bias for selective reporting. Akyol 2006 published in Turkish, reported the fracture outcomes in the discussion section and there was no relevant information to verify if they were reported properly. In Yanik 2008 (another Turkish study), only one outcome, serious adverse events, was extracted from "serious side effects"(as translated). It was not clear if this meant the same as the outcome "serious adverse events" or whether there were any pre-planned outcomes that might have been missed.

In NCT00365456, all of the outcome data were extracted from the database of clinicaltrials.gov. Galesanu 2011 was published in an abstract where the information for comparing whether the outcomes were reported as pre-planned was less than sufficient. These three studies were judged to be at unclear risk of bias.

Two studies were judged to be at high risk. McClung 2001 combined two daily doses of risedronate (2.5 mg and 5 mg) when reporting fracture outcomes. It was unclear as to whether this was pre-planned and it precluded the independent assessment of each dose. One study Muscoso 2004 was judged to have high risk of reporting bias because it did not report any information about safety which did not met the reporting practice of clinical trials.

#### Other potential sources of bias

In this domain, all of the included studies were judged to be at low risk of bias except for 11 at unclear risk. In the Dobnig 2006 study, participants randomised to bisphosphonate treatment received daily doses of either alendronate (10 mg /day) or risedronate (5 mg/day). It appeared as if the use of either risedronate or alendronate was not randomised and the two treatments were analysed as one, but there was insufficient detail to make a judgment. Ten studies were judged to be at unclear risk of bias due to limited information. In Fogelman 2000, Harris 1999 and Reginster 2000, for example, the risedronate 2.5 mg arm was discontinued early due to protocol amendment. In Paggiosi 2014a, a large drop-out rate reported in the second-year extension does not appear to have been pre-planed before the study launched. It is not clear if these changes biased the results. Two Turkish studies, Akyol 2006 and Yanik 2008, were translated into English by an online translation service and were difficult to interpret. Galesanu 2011 was published in abstract form. Muscoso 2004 reported very limited information. Reid 2006 offered recruited participants the option to re-consent before entering the second year extension period, for which only 72 of the original 75 international sites chose to participate. Although the study design was maintained and the treatments remained randomised, it is not clear whether this option would have led to bias. For NCT00365456, the information was only available in the trial registry website which was insufficient to make a judgment.

#### *Summary assessment of risk of bias*

For the 33 studies included in the quantitative syntheses, five domains of ROB were assessed. "Random sequence generation" and "allocation concealment" were the most frequently overlooked, with 73% of the studies failing to meet the low risk criteria in one or the other of these domains. Only eight studies were judged to be at low risk of bias in both, and were considered to perform randomisation properly. For the domain of performance bias, 64% of the studies were subject to unclear (12%) and high risk of bias (52%) due to the lack of appropriate blinding methods. The criteria for "selective reporting" and "other bias" were properly fulfilled by 82% (27/33) and 67% (22/33) of the studies.

The assessments for the remaining two domains were only conducted for the studies reporting data for the outcome group being assessed (i.e. subjective and objective outcomes for detection bias, and safety and efficacy outcomes for attrition bias). Twenty-two studies (100%) reporting objective outcomes were judged at low risk of detection bias regardless of the blinding method. Among the 29 studies reporting at least one subjective outcome, 13 (45%) were considered to effectively blind the participants and outcome assessors, while 16 (55%) were subject to unclear and high risk of detection bias for the lack of sufficient blinding methods. For "attrition bias", 73% (16/22) and 55% (17/31) of the studies were judged to be at unclear or high risk of bias for efficacy and safety outcomes, respectively.

None of the 33 studies included in the quantitative syntheses were judged to be at low risk of bias in all seven domains.

## Effects of interventions

See: **Summary of findings 1** Risedronate 5 mg/day compared to placebo for the primary prevention of osteoporotic fractures in postmenopausal women; **Summary of findings 2** Risedronate 5 mg/day compared to placebo for the secondary prevention of osteoporotic fractures in postmenopausal women

#### Base-case analyses

#### *Risedronate 5 mg/day versus placebo*

For six major outcomes, including clinical vertebral, non-vertebral, hip and wrist fractures, withdrawals due to adverse events, and serious adverse events, four primary (989 participants) and nine secondary (14,354 participants) studies reported data for daily risedronate 5 mg comparing with placebo. The results for primary and secondary prevention are summarised in Table 2, and Summary of findings 1 and Summary of findings 2, respectively.

##### Major outcomes

**Clinical vertebral fractures (**Analysis 1.1)
Clinical vertebral fractures were reported in one primary (Välimäki 2007) and two secondary prevention trials (Leung 2005; Li 2005). However, zero events were inferred from the text of the papers

and the risk ratio (RR) was not estimable. For both primary and secondary prevention, the effects of risedronate 5 mg/day on clinical vertebral fractures are unclear based on the limited evidence of low certainty.

**Non-vertebral fractures** *(*Analysis 1.2*)*

Three primary prevention trials (Hooper 2005; Mortensen 1998; Välimäki 2007) reported seven among 281 risedronate-treated and 11 among 216 placebo-treated women sustained non-vertebral fractures. With minimal heterogeneity ($I^2$ = 0%) and a pooled estimate of RR 0.54 (95% CI 0.22 to 1.35), we were unable to reject the null hypothesis. We don't know if risedronate 5 mg/day reduces non-vertebral fractures because the certainty of this evidence is very low.

For secondary prevention studies, six trials (Fogelman 2000; Harris 1999; Leung 2005; Li 2005;McClung 2001; Reginster 2000) consistently ($I^2$ = 0%) demonstrated the benefit of risedronate in reducing non-vertebral fractures. In total, 8.7% (659 among 7614 women) risedronate-treated and 10.2% (467 among 4559 women) placebo-treated women sustained non-vertebral fractures. The pooled estimate of the RR was 0.80 (95% confidence interval (CI) 0.72 to 0.90), in which McClung 2001 accounted for 80% of the weight of the evidence thus dominating the estimate for RR) Based on the moderate-certainty evidence, a reduction of 20% (95% CI 10% to 28%) from risedronate 5 mg/day is probably clinically important. The absolute risk reduction (ARR) and number needed to treat for an additional beneficial outcome (NNTB) were estimated as 2% (95% CI 1% to 3%) and 50 (95% CI 35% to 98%), respectively.

Corresponding to the important benefit of relative risk reduction (RRR) 20%, the absolute measures ARR and NNTB of the five-year risk of non-vertebral fracture after treatment with risedronate were calculated for different levels of increasing risk as given by the fracture index (FI) (Table 3) and for increasing age (Table 4). For the illustrative case of the patient with a FI of 6 to 7, the ARR in non-vertebral fracture was 4.0% (that is, a reduction in risk from 19.8% to 15.8%) and the NNTB was 25 (that is, 25 patients need to be treated to avoid one non-vertebral fracture). Across the range of increasing FI risk, the ARR for non-vertebral fracture ranged from 1.7% to 5.5% and the NNTB to avoid one non-vertebral fracture ranged from 58 to 18. For the illustrative patient in the age group 60 to 64 years, the ARR for the first non-vertebral fracture was 0.6% (i.e. a reduction in risk from 3.1% to 2.5%) and the NNTB was 161 (that is, 161 patients need to be treated to avoid the first fracture). The ARR for a subsequent fracture was 1.2% (that is, a reduction in risk from 6.2% to 5.0%) and the NNTB was 81 patients who need to be treated to avoid one subsequent fracture. For increasing age, the five-year age-specific ARR for the first non-vertebral fracture increased from 0.3% for the youngest age group (50 to 54 years) to 7.0% in the highest age group (90+ years). Accordingly, the NNTB decreased from 313 to 14. For the subsequent fracture, ARR increased from 0.5% to 7.5% and NNTB decreased from 192 to 13 for youngest and highest age group, respectively.

**Hip fractures (**Analysis 1.3)

For primary prevention, two trials (Mortensen 1998; Välimäki 2007) reported this outcome with zero women sustaining a hip fracture. The effect of risedronate 5 mg/day on hip fracture is unclear based on the limited evidence of low certainty.

Three secondary prevention trials reported this outcome (Leung 2005; Li 2005; McClung 2001), two of which stated that zero fractures had occurred. The estimate of the RR 0.73 (95% CI 0.56 to 0.94) was dominated by the one remaining study McClung 2001, in which 137 among 6256 women receiving risedronate (2.2%) and 95 among 3194 receiving placebo (3.0%) sustained at least one hip fracture. Based on the evidence of low certainty, the RRR, ARR and NNTB was 27% (95% CI 6% to 44%), 1% (95% CI 0.2% to 1%) and 127 (76 to 560), respectively. Risedronate 5 mg/day may reduce hip fractures and the reduction is probably clinically important.

Corresponding to the important risk reduction 27%, the absolute measures ARR and NNTB of the five-year risk of hip fracture after treatment with risedronate were calculated for different levels of increasing risk as given by the FI (Table 3), and for increasing age (Table 4). For the illustrative case of the patient with a FI of 6 to 7, the ARR for hip fracture was 1.1% (that is, a reduction in risk from 3.9% to 2.8%) and the NNTB was 95 (that is, 95 patients need to be treated to avoid one hip fracture). Across the range of increasing FI risk, the ARR for hip fracture ranged from 0.1% to 2.3% and the NNTB to avoid one hip fracture ranged from 926 to 43. For the illustrative patient in the age group 60 to 64 years, the ARR for the first hip fracture was 0.1% (i.e. a reduction in risk from 0.2% to 0.1%) and the NNTB was 1852 patients treated to avoid the first fracture. The ARR and NNTB for a subsequent fracture were the same. For increasing age, the five-year age-specific ARR for the first hip fracture increased from less than 0.05% for the youngest age group (50 to 54 years) to 5.6% in the highest age group (90+ years) and the NNTB decreased from more than 1852 to 18. For the subsequent fracture, ARR increased from less than 0.05% to 6.2% and the NNTB decreased from more than 926 to 16 for youngest and highest age group, respectively.

**Wrist fractures (**Analysis 1.4)

Wrist fractures were reported in two primary prevention trials (Mortensen 1998; Välimäki 2007), with one participant each in the risedronate (152 women) and placebo groups (91 women). We were unable to reject the null hypothesis given that the risk estimate for RR 0.48, 95% CI 0.03 to 7.50) also includes no effect. Risedronate 5 mg/day may reduce wrist fractures. However, the 95% confidence interval indicates that risedronate might make little or no difference. The evidence was assessed as low certainty.

Three secondary prevention trials reported this outcome (Harris 1999; Leung 2005; Li 2005), two of which were inferred to have zero wrist fractures from the text of the papers. The RR 0.64 (95% CI 0.33 to 1.24) was estimated from the remaining study, Harris 1999, in which 14 among 871 women receiving risedronate (1.6%) and 22 among 875 receiving placebo (2.5%) sustained at least one wrist fracture. The null hypothesis cannot be rejected on the basis of the risk reduction (36%) suggested in this study. We don't know if risedronate 5 mg/day reduces wrist fractures because the certainty of this evidence is very low.

**Withdrawals due to adverse events (**Analysis 1.6**)**

For primary prevention, three trials (Bala 2014; Hooper 2005; Välimäki 2007) reported a total of 23 among 465 risedronate-treated and 21 among 283 placebo-treated participants withdrew from the study due to adverse events. The pooled estimate of the RR was 0.67 (95% CI 0.38 to 1.18). Risedronate 5 mg/day may reduce withdrawals due to adverse events. However, the 95%

confidence interval indicates that risedronate might make little or no difference. The evidence was assessed as low certainty.

For secondary prevention, eight trials (Dobnig 2006; Dundar 2009; Fogelman 2000; Harris 1999; Hosking 2003; Li 2005; McClung 2001; Reginster 2000) reported a total of 806 and 811 early discontinuations for adverse events in the risedronate (4815 women) and placebo (4714 women) groups, respectively. Based on the high-certainty evidence, the pooled estimate of the RR 0.98 (95% CI 0.90 to 1.07) demonstrates that risedronate 5 mg/day slightly reduces withdrawals due to adverse events. However, the 95% confidence interval indicates that risedronate might make little or no difference.

**Serious adverse events (**Analysis 1.7**)**

Two primary prevention trials (Hooper 2005; Välimäki 2007) reported 24 women in the risedronate group (9.8%) and 25 women in the placebo group (13.9%) had serious adverse events, for which the pooled RR was estimated to be 0.74 (95% CI 0.42 to 1.30). However, substantial heterogeneity was suspected given that the $I^2$ value was 70 % and the non-significant test for heterogeneity P value was 0.07. Although both studies were defined as primary prevention, Välimäki 2007 appeared to include menopausal women with a higher risk of fractures than Hooper 2005. The former included only menopausal women with osteopenia so the mean lumbar spine BMD T-score was lower than that in the latter [-1.82 (SD 0.42) versus -0.40 (SD 0.17)]. In addition, the population in Välimäki 2007 was older [mean age 65.9 (6.8) versus 52.7 (1.8)]. The risk of serious adverse events observed in Hooper 2005 was 17.6% (22 among 125 women) in placebo and 9.3% (12 among 129 women) in the risedronate arm; while in Välimäki 2007, 5.5% (3/55) of the placebo-treated versus 10.4% (12/155) of the risedronate-treated experienced serious adverse events. The individual effect sizes for the two studies were different in both magnitude and direction (RR 0.53, 95% CI 0.27 to 1.02 in Hooper 2005 versus RR 1.91, 95% CI 0.56 to 6.50 in Välimäki 2007).

Overall for primary prevention, we do not know if risedronate 5 mg/day reduces serious adverse events because the certainty of this evidence is very low.

Six secondary prevention trials (Fogelman 2000; Harris 1999; Hosking 2003; Leung 2005; McClung 2001; Reginster 2000) reported the outcome of serious adverse events. In total, 1372 risedronate-treated and 1366 placebo-treated participants experienced at least one incident. Both risedronate and placebo demonstrated the same risk with the estimated RR of 1.00 (95% CI 0.94 to 1.07). Based on the evidence graded as moderate certainty, risedronate 5 mg/day probably makes little or no difference to serious adverse events for postmenopausal women at higher risk of fractures.

In addition, two three-year secondary prevention trials reported major outcomes for risedronate during extensional periods but were not included in the base-case analyses. Although the original randomised treatments and blinding were maintained through the extension, there was considerable attrition. It is also not clear whether the fractures reported during the two-year extension period were first or subsequent fractures. In Harris 1999, 9.1% (4/44) and 4.5% (2/44) women receiving risedronate (originally randomised 817 participants) and 7.1% (3/42) and 16.7% (7/42) women receiving placebo (originally randomised 820 participants) experienced radiographic vertebral and non-vertebral fractures, respectively. Zero risedronate-treated and three placebo-treated participants withdrew the study due to adverse events. In Reginster 2000, 13.8% (15/109) and 5.2% (7/135) women receiving risedronate (408 participants originally randomised) and 28.2% (29/103) and 8.5% (11/129) receiving placebo (408 participants originally randomised) experienced radiographic vertebral and non-vertebral fractures, respectively. During years four and five, 33 risedronate-treated (24.4%) and 39 placebo-treated participants (30.0%) withdrew the study due to adverse events, and ten risedronate-treated (7.4%) and 16 placebo-treated participants (12.3%) experienced serious adverse events.

#### Minor outcomes

For minor outcomes, data were only available for radiographic vertebral fractures, gastrointestinal adverse effects and atypical femoral fractures which were extracted from two primary (Hooper 2005; Välimäki 2007) and seven secondary (Fogelman 2000; Harris 1999; Hosking 2003; Leung 2005; Li 2005; McClung 2001; Reginster 2000) prevention studies. The results are summarised in Table 5.

**Radiographic vertebral fractures *(*Analysis 1.5*)***

For primary prevention, two studies reported data. Mortensen 1998 reported zero fractures, while Hooper 2005 reported 10 radiographic vertebral fractures each in the risedronate 5 mg/day and placebo groups. The estimate of the RR was 0.97 (95% CI 0.42 to 2.25), and the ARR was 0.2% fewer (95% CI 4% fewer to 8% more). We do not know if risedronate reduces radiographic vertebral fracture because the certainty of this evidence is very low.

Three secondary prevention trials reported data for radiographic vertebral fractures (Fogelman 2000; Harris 1999; Reginster 2000). In total, 122 and 199 radiographic vertebral fractures were reported in the risedronate 5 mg/day and placebo groups, respectively. Based on the evidence of moderate certainty, the pooled estimate of the RR (0.61, 95% CI 0.50 to 0.75) indicates that risedronate 5 mg/day probably results a clinically important reduction (39%, 95% CI 25% to 50%) in radiographic vertebral fractures, with an ARR of 7% (95% CI 4% to 9%) and NNTB of 15 (95% CI 12 to 23).

Corresponding to the important RRR of 39% in radiographic vertebral fractures from the secondary prevention trials, the absolute measures ARR and NNTB of the five-year risk of vertebral fracture after treatment with risedronate 5 mg/day were calculated for different levels of increasing risk as given by the FI. Results are provided in Table 3 as well as for increasing age in Table 4.

For the illustrative case of the patient with a FI of 6 to 7, the ARR in vertebral fracture was 2.8% (that is, a reduction in risk from 7.1% to 4.3%) and the NNTB was 36 (that is, 36 patients 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 0.5% to 4.4% and the NNTB to avoid one vertebral fracture ranged from 214 to 23. For the illustrative patient in the age group 60 to 64 years, the ARR for the first radiographic vertebral fracture was 0.4% (that is, a reduction in risk from 1.0% to 0.6%) and the NNTB was 256 (that is, 256 patients need to be treated to avoid the first fracture. The ARR for a subsequent fracture was 3.8% (that is, a reduction in risk from 9.7% to 5.9%) and the NNTB was 26 (that is, 26 patients 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 1.8% in the highest

age group (90+ years) and the NNTB decreased from 1282 to 55. For subsequent fractures, ARR increased from 0.2% to 10.9% and the NNTB decreased from 513 to 9.

**Gastrointestinal adverse events (**Analysis 1.8**)**

Two primary prevention trials (Hooper 2005; Välimäki 2007) reported 46 participants (18.9%) receiving risedronate and 34 participants (18.9%) receiving placebo experienced gastrointestinal adverse events. The estimated RR was 0.97 (95% CI 0.66 to 1.44), which indicated that risedronate makes little or no difference to this outcome.

For secondary prevention, six trials (Fogelman 2000; Harris 1999; Hosking 2003; Leung 2005; McClung 2001; Reginster 2000) reported 1113 among 4754 risedronate-treated participants (23.4%) experienced gastrointestinal adverse events. Compared with 1084 events observed in the placebo group (23.2% of 4680 participants), risedronate appeared to have similar risk (RR 1.01, 95% CI 0.93 to 1.08) with placebo.

**Atypical femoral fracture (**Analysis 1.9**)**

Among all placebo-controlled trials of risedronate 5 mg/day, only one primary (Välimäki 2007) and two secondary (Harris 1999; Li 2005) prevention studies reported the outcome of atypical femoral fracture. Zero participants sustained a femoral fracture so neither the RR for primary or secondary prevention was estimable.

***Risedronate 2.5 mg/day versus placebo***

Data for risedronate 2.5 mg/day compared to placebo were extracted primarily from four three-arm placebo-controlled studies, including one primary (Hooper 2005) and three secondary prevention trials (Fogelman 2000; Harris 1999; Reginster 2000). The only fracture outcomes reported were non-vertebral and radiographic vertebral. All of the three secondary prevention trials discontinued the risedronate 2.5 mg/day arm due to protocol amendment, including one after the first year (Harris 1999), one at two years (Reginster 2000), and one at 9 out of the 13 centres (Fogelman 2000). Two additional secondary prevention studies (McClung 2001; Ohtori 2013 ) reported the comparison of risedronate 2.5 mg/day versus placebo for withdrawals due to adverse events and serious adverse events. The comparisons are presented in Analysis 9.1 and Analysis 9.5 and results summarised in Table 5 and Table 6.

**Major outcomes**

**Non-vertebral fractures (**Analysis 9.1*)*
Only one primary prevention trial (Hooper 2005) reported non-vertebral fractures. The estimated RR 0.49 (95% CI 0.13 to 1.92) indicates that risedronate 2.5 mg/day may lead to fewer incidents. However, the effects vary and it is possible that risedronate 2.5 mg/day makes little or no difference to this outcome.

Three secondary prevention trials (Fogelman 2000; Harris 1999; Reginster 2000) reported non-vertebral fractures, with 46 of 1139 risedronate-treated (4%) and 66 of 1242 placebo-treated women (5.3) sustaining a fracture. The pooled estimate of the RR (RR 0.80, 95% CI 0.55 to 1.16), though homogeneous across studies ($I^2$=0), did not demonstrate a risk reduction with sufficient certainty.

**Withdrawals due to adverse events (**Analysis 9.3**)**

One primary prevention study, Hooper 2005 reported 12 and 8 participants in the risedronate (127 women) and placebo (125 women) groups, respectively, withdrew from the study due to adverse events. The estimate of RR 1.48 (95% CI 0.62,3.49) demonstrated that risedronate probably makes little or no difference to this outcome.

For secondary prevention, four trials (Harris 1999; McClung 2001; Ohtori 2013; Reginster 2000) in total reported that 690 among 4332 risedronate-treated participants and 783 among 4378 placebo-treated participants discontinued early because of adverse events. The pooled estimate of the RR for risedronate compared to placebo was 0.89 (95% CI 0.81 to 0.98). However, the percentage of the variability in effect estimate that was due to heterogeneity rather than chance was observed to be as high as 85%, with a P value of 0.001 for the non-significant test. The considerable differences between studies might be attributed to the early withdrawals of the risedronate 2.5 mg/day arm in Harris 1999 and Reginster 2000 due to protocol amendment, which may have resulted in a lower incidence of withdrawals due to adverse events in these arms. The incidence of withdrawals due to adverse events for risedronate 2.5 mg was lower in Harris 1999 (89/811, 11.0%) and Reginster 2000 (53/408, 13.0%), but higher in McClung 2001 (548/3093, 17.7%). If compared with placebo, evidence from both Harris 1999 and Reginster 2000 demonstrated that daily risedronate 2.5 mg resulted in a reduction in withdrawals adverse events (RR 0.66, 95% CI 0.51 to 0.84 and RR 0.64, 95% CI 0.46 to 0.87, respectively); while in McClung 2001, little or no difference was observed (RR 0.98, 95% CI 0.89 to 1.10).

**Serious adverse events (**Analysis 9.4**)**

For primary prevention, 13 and 22 participants in the risedronate and placebo groups, respectively, experienced serious adverse events during the study period (Hooper 2005). Risedronate 2.5 mg/day appeared to reduce the risk but the estimated RR was RR 0.58 (95% CI 0.31 to 1.10), indicating that it probably had little or no effect.

In three secondary trials (McClung 2001; Ohtori 2013; Reginster 2000), serious adverse events were reported for 1070 among 3521 participants receiving risedronate and 1108 among 3563 participants receiving placebo. Both risedronate 2.5 mg/day and placebo had similar risks (RR 0.98, 95% CI 0.91 to 1.05) for this outcome.

**Minor outcomes**

**Radiographic vertebral fractures (**Analysis 9.2)
For primary prevention, only one study (Hooper 2005) reported the outcome of radiographic vertebral fractures. The estimate of the RR showed that risedronate 2.5 mg/day was not better than placebo in preventing this outcome (RR 1.08, 95% CI 0.48 to 2.46).

Radiographic vertebral fractures were reported in three secondary prevention trials (Fogelman 2000; Harris 1999; Reginster 2000). In total, 51 of 926 participants receiving risedronate 2.5 mg/day and 99 of 1068 participants receiving placebo sustained radiographic vertebral fractures. Without notable heterogeneity across studies (P = 0.48), the pooled estimate of the RR 0.63 (95% CI 0.45 to 0.87) demonstrated a risk reduction of 37% (95% CI 13% to 55%), which is probably clinically important.

Corresponding to the estimated RRR of 37% for the secondary prevention of radiographic vertebral fractures, the absolute measures ARR and NNTB of the five-year risk of vertebral fracture after treatment with risedronate were calculated for different levels of increasing risk as given by the FI. Results are provided in Table 3, as well as for increasing age in Table 4. For the illustrative case of the patient with a FI of 6 to 7, the ARR in radiographic vertebral fracture was 2.6% (that is, a reduction in risk from 7.1% to 4.5%) and the NNTB was 38 (that is, 38 patients 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 0.4% to 4.1% and the NNTB to avoid one radiographic vertebral fracture ranged from 225 to 24. For the illustrative patient in the age group 60 to 64 years, the ARR for the first radiographic vertebral fracture was 0.4% (that is, a reduction in risk from 1.0% to 0.6%) and the NNTB was 270 patients treated to avoid the first fracture. The ARR for a subsequent fracture was 3.6% (that is, a reduction in risk from 9.7% to 6.1%) and the NNTB was 28 patients 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 1.7% in the highest age group (90+ years) and the NNTB decreased from 1351 to 58. For subsequent fractures, ARR increased from 0.2% to 10.3% and the NNTB decreased from 541 to 10.

**Gastroinstestinal adverse events (**Analysis 9.5**)**

The only other minor outcome with data available for risedronate 2.5 mg/day versus placebo was gastrointestinal adverse events. One primary prevention study, Hooper 2005, reported that 26 risedronate and 20 placebo-treated participants suffered from upper gastrointestinal adverse events during the treatment period. Risedronate appeared to have little or no effect on this outcome (RR 1.28, 95% CI 0.75 to 2.17).

Likewise, for secondary prevention, the risk of gastrointestinal complaints was similar in both groups (risedronate: 784/3501, 22.4%; placebo: 788/3543, 22.2%), based on the pooled data of two trials (McClung 2001; Reginster 2000). The estimate for RR was (RR 1.01, 95% CI 0.93 to 1.10).

**Subgroup analyses**

***Risedronate 5 mg/day versus placebo***

To further investigate if the anti-fracture effects of daily risedronate 5 mg would vary by treatment duration or for participants with prior bisphosphonate experience, we conducted the following subgroup analyses for five fracture outcomes, including clinical vertebral, non-vertebral, hip, wrist, and radiographic vertebral fractures.

***Different treatment durations***

The anti-fracture effects of risedronate 5 mg/day were analysed for the following durations: one year (Analysis 2.1 to Analysis 2.5), two years (Analysis 3.1 to Analysis 3.5) and three years (Analysis 4.1 to Analysis 4.4). Most of the effects of risedronate 5 mg/day were investigated from one to three years in the included RCTs. Consistent with the base-case results for the primary prevention trials, risedronate 5 mg/day did not appear to reduce fracture risk at any anatomic locations over different treatment durations. However, in the secondary prevention trials, risedronate 5 mg/day showed promising anti-fracture effects after one, two and three years of treatment (Table 7).

For primary prevention which had scant evidence for all fracture outcomes, data were only available for up to two years of treatment. The estimable risedronate effects were only observed for non-vertebral fracture after one year, and for non-vertebral, wrist, and radiographic vertebral fractures after two years. Risedronate consistently demonstrated little or no difference over placebo, as observed in the base case. For postmenopausal women at lower risk of fractures, risedronate does not appear to reduce the risk for up to two years of treatment. Whether risedronate's anti-fracture effects would vary by treatment duration is not known.

For secondary prevention, the magnitude of risedronate effects appeared to decrease over the years for non-vertebral and radiographic vertebral fractures. For the former, the important risk reduction of 33% (RR 0.67, 95% CI 0.49 to 0.91) at year two was decreased to 19% (RR 0.81, 95% CI 0.72 to 0.91) at year three. For the latter, risedronate resulted in important risk reductions of 60% (RR 0.40, 95% CI 0.27 to 0.59), 52% (RR 0.48, 95% CI 0.36 to 0.64) and 38% (RR 0.62, 95% CI 0.50 to 0.77) after one, two, and three years, respectively. For hip and wrist fractures, since the estimable effects in the base case were mainly provided by the 3-year studies, similar results were found for the third year; while at years one and two, outcome data were either not available or not estimable. For postmenopausal women at higher risk of fractures, risedronate 5 mg/day probably results in a reduction in non-vertebral fractures after two years of treatment, which would be continued into the third year although with a slight decrease. However for hip fractures, specifically, it probably takes three years for risedronate to prevent an incidence. Risedronate probably makes little or no difference to clinical vertebral and wrist fractures regardless of treatment duration. It probably reduces radiographic vertebral fracture after one-year treatment and remains effective up to three years, although the magnitude of the effect slightly decreases with time.

***Prior bisphosphonate experience (***Analysis 5.1 to Analysis 5.5; Table 7***)***

Only one primary (Hooper 2005) and two secondary prevention studies (Li 2005; Reginster 2000) reporting any fracture outcome recruited bisphosphonate-naïve participants exclusively; and no study included only bisphosphonate-experienced participants. Therefore, subgroup analysis taking participants' prior bisphosphonate experience into consideration was only available for bisphosphonate-naive patients.

For primary prevention, the estimable RRs suggested risedronate made little or no difference to non-vertebral and radiographic vertebral fractures for postmenopausal women who reported never having been exposed to a bisphosphonate, similar to what was observed in the base-case scenario.

For secondary prevention, risedronate also resulted in an important risk reduction in radiographic vertebral fracture for women naïve to bisphosphonate (RR 0.60, 95% CI 0.44 to 0.81), similar to that in the base case (RR 0.61, 95% CI 0.50 to 0.75). However, risedronate did not duplicate its effects (RR 0.80, 95% CI 0.72 to 0.90) in preventing non-vertebral for bisphosphonate-naïve women (RR 0.71, 95% CI 0.47 to 1.06), which, nevertheless, might be explained by the loss of evidence (12,173 participants in the base case versus 866 bisphosphonate-naïve participants).

Based on the limited evidence, we were not able to investigate whether risedronate's anti-fracture effects would be influenced by participant's prior bisphosphonate experience.

***Risedronate 2.5 mg/day versus placebo***

***Different treatment durations*** *(*Analysis 10.1 to Analysis 10.2; Analysis 11.1 to Analysis 11.2; Table 8 *)*

For primary prevention, only one two-year study (Hooper 2005 ) reported fracture outcome data. The estimated RRs in non-vertebral and radiographic vertebral fractures for two years of treatment were the same as those for base case.

For secondary prevention, for non-vertebral fractures, neither one (RR 0.87, 95% CI 0.56 to 1.36) or two years (RR 0.73, 95% CI 0.44 to 1.22) of risedronate 2.5 mg/day showed different risks from placebo with sufficient certainty. Similar results did not demonstrate any trend over years of risedronate treatment. Risedronate 2.5 mg/day was likely to reduce the risk for radiographic vertebral fractures after one year (RR 0.63, 95% CI 0.45 to 0.87). This effect appeared to continue for the second year of treatment, although the evidence was less certain (RR 0.66, 95% CI 0.43 to 1.01).

***Prior bisphosphonate experience*** *(*Analysis 12.1 to Analysis 12.2*;* Table 8*)*

The only primary prevention trial available for the 2.5 mg base case had exclusively recruited bisphosphonate-naive participants. Therefore, the relative risk for the subgroup analysis was the same as that in the base case.

For secondary prevention, one of three trials had exclusively included bisphosphonate-naive participants (Reginster 2000). For non-vertebral fractures, risedronate's effect was not supported with sufficient certainty (RR 0.88, 95% CI 0.50 to 1.53), as observed in the base case (RR 0.80, 95% CI 0.55 to 0.16). However, to prevent radiographic vertebral fractures, risedronate appeared to have a greater effect on those who had never been exposed to any bisphosphonate, with the risk reduction increased from 37% (RR 0.63, 95% CI 0.45 to 0.87) to 43% (RR 0.57, 95% CI 0.34 to 0.95).

**Sensitivity analyses**

***Risedronate 5 mg/day versus placebo***

To test the robustness of the anti-fracture effects of risedronate 5 mg/day demonstrated in the base case analyses, we conducted the following sensitivity analyses (Table 9).

***Follow-up versus baseline denominators*** (Analysis 6.1 to Analysis 6.5)

Baseline denominators (randomised numbers) for patients taking risedronate 5 mg/day and placebo were used for the relative risk calculation of fracture outcomes, which were compared with the results from the base case using follow-up denominators. As summarised in Table 9, the pooled estimates of the RRs of risedronate's anti-fractures effects were similar in both scenarios in terms of the direction, magnitude, and precision of the risk reductions. The results of the base-case analyses appeared robust regardless of the denominators adopted.

***Studies with fracture as an efficacy outcome*** ***(***Analysis 7.1 to Analysis 7.4***)***

Among the base-case analyses, three secondary prevention trials identified fractures as efficacy outcomes (Harris 1999; McClung 2001; Reginster 2000). In these trials, the fracture outcomes were well-defined and confirmed by radiographic/morphometric methods, the statistical strategy was pre-planned appropriately for hypothesis testing, and sufficient power (sample size) was obtained. The available pooled estimates of the RRs of risedronate's anti-fracture effects in secondary prevention were similar to those in the base case in terms of the direction, magnitude, and precision of the risk reductions. The results of the base-case analyses appeared to be consistent with the studies reporting fracture as an efficacy outcome.

***Studies with high methodological quality***

Publications for the three primary and six secondary prevention trials contributing anti-fracture data to the base case were all full text and peer-reviewed. However, none of them were judged to be at low risk of bias in both domains of allocation concealment and incomplete outcome data for efficacy. Therefore, a sensitivity analysis was not required.

***Excluding primary/secondary prevention studies entirely based on the age criterion***

None of the primary and secondary prevention studies included in the base-case analysis were defined by age alone. A sensitivity analysis was not required.

***Excluding*** McClung 2001 ***study from the base-case analysis*** ***(***Analysis 8.1 to Analysis 8.5***)***

The sensitivity analyses excluding McClung 2001 (which combined the 2.5 mg and 5 mg daily doses) from the base-case analysis only involved the pooled estimates in non-vertebral and hip fractures for secondary prevention trials. As summarised in Table 9, the direction and precision of the estimate for risk reductions did not change for non-vertebral fractures, although it was increased from 20% to 34% with a wider CI (from 0.72-0.90 to 0.51-0.86) probably due to the decreased sample size. However for hip fractures, the exclusion of McClung 2001 resulted in a non-estimable RR because the remaining two studies (Leung 2005; Li 2005) reported zero events. The estimated anti-fracture effects of risedronate on non-vertebral fractures appeared robust, while effects on hip could not be tested in this review.

***Risedronate 2.5 mg/day versus placebo***

The robustness of daily risedronate 2.5 mg's anti-fracture effects demonstrated in the base case were examined in the following analyses.

***Follow-up versus baseline denominators (***Analysis 13.1 to Analysis 13.2***;*** Table 8***)***

When using baseline denominators (randomised numbers) instead of follow-up denominators, the estimates of anti-fracture RRs were similar to those calculated for the base case in terms of the direction, magnitude, and precision.

***Studies with fracture as an efficacy outcome*** ***(***Analysis 14.1 to Analysis 14.2***;*** Table 8***)***

None of the primary prevention trials reporting fracture outcomes investigated fractures as an efficacy outcome. No sensitivity analysis was conducted.

For secondary prevention, two trials reported fractures as efficacy outcomes (Harris 1999; Reginster 2000). The estimates of RRs for non-vertebral (RR: 0.81, 95% CI 0.54 to 1.20) and radiographic vertebral fractures (RR: 0.58, 95% CI 0.41 to 0.82) were similar to those in the base case.

***Studies with high methodological quality***

One primary and three secondary prevention trials contributing anti-fracture data for risedronate 2.5 mg/day were peer-reviewed full publications. However, none of them were judged to be at low risk of bias for the domains of allocation concealment and incomplete outcome data-efficacy. No sensitivity analysis was conducted.

***Studies analysis excluding primary/secondary prevention studies entirely based on age criterion***

None of the included primary and secondary prevention studies were defined by age alone. No sensitivity analyses were conducted.

**Risedronate 5 mg/day versus 2.5 mg/day**

The benefits or harms of risedronate 5 mg/day versus 2.5 mg/day were compared in Analysis 15.1 to Analysis 15.4, and the results are summarised in Appendix 6.

For primary prevention, only one study (Hooper 2005) reported outcomes of interest. The effects of the two daily doses of risedronate on non-vertebral fractures, withdrawals due to adverse events, serious adverse events and radiographic vertebral fractures varied, although none of the estimated RRs [1.64 (95% CI 1.40 to 6.72),0.57 (95% CI 0.23 to 1.41), 0.91 (95% CI 0.43 to 1.91) and 0.89 (95% CI 0.39 to 2.03), respectively] enabled us to reject the null hypotheses. Twenty-five among 129 women (19.4%) receiving risedronate 5 mg/day and 26 among 127 women (20.5%) receiving risedronate 2.5 mg/day complained of gastrointestinal adverse events. The estimate for the RR was 0.95 (95% CI 0.58 to 1.55) demonstrated little to no difference.

For secondary prevention, four studies (Fogelman 2000; Harris 1999; McClung 2001; Reginster 2000) reported at least one outcome of interest. For non-vertebral fractures, the effects of risedronate 5 and 2.5 mg/day did not differ (RR 0.85, 95% CI 0.57 to 1.29) (Fogelman 2000; Harris 1999; Reginster 2000). However, risedronate 5 mg/day appeared to have a beneficial risk reduction of 34% for radiographic vertebral fractures compared with the lower daily dose of 2.5 mg (RR 0.66, 95% CI 0.44 to 0.98) (Fogelman 2000; Harris 1999; Reginster 2000).

With respect to withdrawals due to adverse events, considerable heterogeneity ($I^2$=81% and P value= 0.005 for the non-significant test) was observed, which was likely caused by the early termination of the risedronate 2.5 mg/day arm in two (Harris 1999; Reginster 2000) of the three included studies. These protocol amendments may have resulted in fewer withdrawals due to adverse events in the affected arms, compared to the 2.5 mg/day arm of the remaining study, McClung 2001. In total, 753 among 4324 women (17.4%) receiving risedronate 5 mg/day and 690 among 4312 women receiving risedronate 2.5 mg/day withdrew due to adverse events. By study, the risks of these withdrawals for risedronate 5 mg versus 2.5 mg were 17.0% versus 11.0%, 16.0% versus 13.0% and 17.7% versus 17.7%, respectively. In McClung 2001, the effect of both doses appeared to be equivalent for this outcome (RR 1.00, 95% CI 0.90 to 1.11). However, in Harris 1999 and Reginster 2000, daily risedronate 2.5 mg compared to 5 mg appeared to result in fewer withdrawals due to adverse events, with the risk being elevated for the 5 mg dose [RR 1.55 (95% 1.21 to 1.98) and RR 1.23 (95% CI 0.88 to 1.72)].

Again, the methodological difference between two studies (McClung 2001; Reginster 2000) appeared to play into the considerable heterogeneity ($I^2$ = 73% and P value 0.05 for non-significant test) observed in the dose comparison for serious adverse events. In total, 1094 among 3512 women (31.2%) receiving risedronate 5 mg/day and 1070 among 3501 women receiving risedronate 2.5 mg/day respectively experienced an event. By study, the risk of serious adverse events for daily risedronate 5 mg versus 2.5 mg were 37.0% versus 30.4% in Reginster 2000 and 30.4% versus 30.6% in McClung 2001. In the former study, risedronate 5 mg compared to 2.5 mg appeared to increase the risk (RR 1.22, 95% 1.00 to 1.48), while in the latter, both doses appeared to have the same risk (RR 0.99, 95% CI 0.92 to 1.07).

Two different daily doses of risedronate, 5 mg versus 2.5 mg, also made little to no difference to serious adverse events [31.2% versus 30.6%, RR 1.02 (95% CI 0.95 to 1.09)] and gastrointestinal adverse events [21.8% versus 22.4%, RR 0.97 (95% CI 0.89 to 1.06)].

**Risedronate 5 mg/day versus the therapeutic equivalents**

The comparison of risedronate 5 mg/day versus its therapeutic equivalents are presented in Analysis 29.1 to Analysis 29.12. Detailed results are summarised in Table 2 in Appendix 5.

The only primary prevention trial (Gu 2015) did not observe any new fractures in women treated with risedronate at either 5 mg/day or 35 mg/week. The study also found little or no difference between the two dose regimens with respect to withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, and osteonecrosis of the jaw.

However, Gu 2015 reported the only woman treated with risedronate 5 mg/day who developed an osteonecrosis of the jaw. The rare event was judged to be a partial necrosis of the left mandible after a tooth extraction and the symptoms resolved after dental treatment. Among all risedronate users, the risk of this outcome was 0.3% (1 among 144 receiving daily 5 mg and 145 weekly 35mg). According to an Australian study, the minimum and maximum frequencies of osteonecrosis of the jaw for patients with osteoporosis who were taking a bisphosphonate and had a dental extraction were 0.09% (1/1130) and 0.03% (1/296), respectively (Mavrokokki 2007).

Four secondary prevention, four studies reported at least one outcome of interest (Brown 2002; Delmas 2008a; Delmas 2008b; McClung 2012). The null hypotheses of no difference between risedronate 5 mg/day and its therapeutical equivalents (35 mg/week, 75 mg on two consecutive days each month and 150 mg/month) in the benefits and harms were not rejected, except for two exceptions. Fewer women treated with daily 5 mg versus monthly 150 mg experienced serious adverse events. The estimate of the RR was 0.67 (95% CI 0.48 to 0.94). Delmas 2008b observed

that fewer women receiving daily risedronate (5 mg) than those receiving monthly risedronate (150 mg) experienced acute phase reactions, with the RR of 0.11 (95% CI 0.01 to 0.89). It is worth noting that, the outcome of acute phase reaction has been more frequently related to intravenous aminobisphosphonates (Olson 2007) so was not investigated in any placebo-controlled study of risedronate included this review. The monthly use of risedronate 150 mg, however, was found to increase the risk of acute phase reaction compared to risedronate 5 mg/day.

**Risedronate versus other anti-osteoporotic agents**

**Primary prevention (**Analysis 16.1; Analysis 17.1; Analysis 18.1; Analysis 19.1; Analysis 20.1; Analysis 21.1; Analysis 22.1**;** Analysis 24.1; Analysis 25.1**)**

Three primary prevention studies (Harris 2001; Muscoso 2004; Rosen 2005) reported data but none of it was comparable for pooling. Harris 2001 compared the combined use of risedronate 5 mg/day and daily conjugated equine estrogens 0.625 mg (HRT) with HRT alone, for which two and seven non-vertebral fractures (RR 0.28, 95% CI 0.06 to 1.35), zero and zero hip and atypical femoral fractures (RR not estimable), zero and one wrist fractures (RR 0.33, 95% CI 0.01 to 8.08), three and four radiographic vertebral fractures (RR 0.69, 95% CI 0.16 to 3.04), 27 and 49 withdrawals due to adverse events (RR 0.55, 95% CI 0.35 to 0.85), 14 and 23 serious adverse events (RR 0.60, 95% CI 0.32 to 1.15), and 43 and 43 gastrointestinal adverse events (RR: 0.99, 95% CI 0.67 to 1.46) were reported. All of the estimable RRs suggested that risedronate contributed little or no additional benefit or harm to the use of HRT with one exception: the combined use of risedronate and HRT (10.2%) appeared to reduce the withdrawals due to adverse events than HRT alone (18.8%).

Muscoso 2004 provided pair-wise comparison data for daily risedronate (5 mg) versus daily raloxifene (60 mg) and weekly intramuscular clodronate (100 mg). However, zero clinical vertebral, non-vertebral, hip and wrist fractures were reported across groups and there was no estimable effect. Rosen 2005 compared weekly use of risedronate 35 mg with alendronate 70 mg and reported similar safety profiles in both groups, including withdrawals due to adverse events (RR 1.01, 95% CI 0.63 to 1.60), serious adverse events (RR 1.09, 95% CI 0.77 to 1.55) and gastrointestinal adverse events (RR 0.92, 95% CI 0.72 to 1.18).

**Secondary prevention**

Nineteen secondary prevention trials (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Dobnig 2006; Fukunaga 2002; Galesanu 2011; Hadji 2012; Hosking 2003; Kasukawa 2014; Kendler 2018; Nakamura 2013; NCT00365456; Ohtori 2013; Paggiosi 2014a; Reid 2006; Roux 2014; Sarioglu 2006; Tanaka 2017; Yanik 2008) comparing risedronate with other osteoporotic agents reported at least one outcome of interest. Data were only pooled when risedronate was compared with alendronate, ibandronate, teriparatide or combined with menatetrenone for some of the outcomes. The results for major and minor outcomes were, respectively, summarised in Table 1 and 2 in Appendix 7. The followings describe the details of each outcome.

**Clinical vertebral fractures (**Analysis 16.2**)**

Three studies compared risedronate [two 35 mg/week (Akyol 2006; Galesanu 2011) and one 5 mg/day (Sarioglu 2006)] with alendronate 70 mg/week, two studies compared risedronate 35 mg/week with ibandronate 150 mg/month (Galesanu 2011; Paggiosi 2014a), and one study compared risedronate 5 mg/day with raloxifene 60 mg/day. Zero participants in these studies experienced a wrist fracture so there was no estimable RR for the comparisons.

In Roux 2014, one participant receiving denosumab 60 mg/6 months (429 women) and 0 receiving risedronate 150 mg/month (429 women) sustained a clinical vertebral fracture, but with an estimated RR 0.33 (95% CI 0.01 to 8.16), we failed to reject the null hypothesis.

**Non-vertebral fractures (**Analysis 17.2**)**

Daily or weekly risedronate was compared with bisphosphonates, including alendronate 70 mg/week (Akyol 2006; Galesanu 2011; Sarioglu 2006) and ibandronate 150 mg/month (Galesanu 2011), all of which reported zero non-vertebral fractures. When risedronate 35 mg/week was compared to subcutaneous teriparatide 20 µg/day (Hadji 2012; Kendler 2018), the estimated RR was 1.28 (95% CI 0.90,1.82), with which the different effects between risedronate and teriparatide were not supported. At the lower dose of 2.5 mg/day or 17.5 mg/week, risedronate was not found to be different in preventing non-vertebral fracture from etidronate 200 mg/day (Fukunaga 2002) and the combination of risedronate and menatetrenone (Tanaka 2017 ), with estimated RRs of 1.74 (95% CI 0.52 to 5.77) and 1.88 (95% CI 0.66 to 2.13), respectively.

**Hip fractures (**Analysis 18.2**)**

Daily or weekly risedronate was compared with bisphosphonates, including alendronate 70 mg/week (Akyol 2006; Galesanu 2011; Paggiosi 2014a; Sarioglu 2006) and ibandronate 150 mg/month (Galesanu 2011; Paggiosi 2014a), all of which reported zero incidents so there was no estimable RR. One study (Roux 2014) found the monthly use of risedronate 150 mg and the subcutaneous denosumab 60 mg twice a year had the same effect (RR 1.00, 95% CI 0.06 to 15.94) in preventing hip fracture. The pooled estimate of the RR from another two studies (Hadji 2012; Kendler 2018) showed that weekly risedronate (35 mg) and daily subcutaneous injection of teriparatide (20 µg) had similar effect (RR 1.01, 95% CI 0.36 to 2.89). For risedronate 17.5 mg/week, used alone or combined with daily menatetrenone 45 mg, zero incidents were observed (Tanaka 2017 ).

**Wrist fractures (**Analysis 19.2**)**

Three studies compared risedronate [two at 35 mg/week (Akyol 2006; Galesanu 2011) and one at 5 mg/day (Sarioglu 2006)] with alendronate 70 mg/week, and one compared weekly risedronate with monthly ibandronate 150 mg (Galesanu 2011). These studies did not observe any wrist fracture. Two studies (Hadji 2012; Kendler 2018), in total, reported three among 1033 weekly risedronate-treated and five among 1043 daily teriparatide-treated women sustained a wrist fracture. The pooled RR of 0.61 (95% CI 0.15 to 2.56) did not allow us to reject the null hypothesis. Zero and one woman treated with risedronate 17.5 mg/week alone and risedronate 17.5 mg/week combined with menatetrenone 45 mg/day were observed to sustain a wrist fracture (Tanaka 2017). The limited evidence did not demonstrate that risedronate alone was different from the combination in reducing the risk for this outcome.

**Withdrawals due to adverse events (**Analysis 21.2**)**

Among active comparisons to risedronate 35 mg/week (or 5 mg/day), data were pooled only when it was compared with alendronate 70 mg/week or 10 mg/day (RR 1.15, 95% CI 0.82 to 1.61) in four studies (Atmaca 2006; Dobnig 2006; Hosking 2003; Reid 2006) and teriparatide 20 µg/day (RR 0.77, 95% CI 0.58 to 1.02) in three studies (Anastasilakis 2008a; Hadji 2012; Kendler 2018). None of these comparisons allowed us to reject the null hypothesis of no difference between treatments. One study, Roux 2014, comparing oral monthly risedronate 150 mg with subcutaneous denosumab 60 mg/6 months found an increased risk estimate of 4.33 (95% 1.24 to 15.10). When weekly risedronate 35 mg was compared with daily PTH 1-84 (NCT00365456), a reduced risk was found, with an estimated RR of 0.24 (95% CI 0.07 to 0.82).

At the lower dose (2.5 mg/day or 17.5 mg/week), risedronate alone demonstrated a risk reduction of 37% over the combined use of risedronate and menatetrenone 45 mg/day. The pooled estimate for the RR was 0.63 (95% CI 0.41 to 0.98) (Kasukawa 2014; Tanaka 2017). Fukunaga 2002 demonstrated that daily risedronate 2.5 mg had a similar risk to that of etidronate 200 mg/day (RR 1.13, 95% CI 0.42 to 3.02). When risedronate 2.5 mg/day was compared to teriparatide 20 µg/day, zero events were reported in both treatments (Ohtori 2013).

**Serious adverse events (**Analysis 22.2**)**

None of the estimable RRs demonstrated a difference in risk with risedronate 35 mg/week (or 5 mg/day or 150 mg/day) for serious adverse events, as compared to alendronate 70 mg/week (or 10 mg/day) (Atmaca 2006; Hosking 2003; Paggiosi 2014a; Reid 2006; Yanik 2008), ibandronate 150 mg/month (Paggiosi 2014a), denosumab 60 mg/6 months (Roux 2014) and teriparatide 20 µg/day (Anastasilakis 2008a; Hadji 2012; Kendler 2018), with the estimated RRs of 1.11 (95% CI 0.80 to 1.54), 1.12 (95% CI 0.44 to 2.89), 1.06 (95% CI 0.67 to 1.67) and 0.95 (95% CI 0.79 to 1.14), respectively. In Yanik 2008, none of the participants in either risedronate 35 mg/week or raloxifene 60 mg/day arm reported a serious adverse event.

In addition, Ohtori 2013 compared oral risedronate 2.5 mg/day with subcutaneous teriparatide 20 µg/day, and reported zero events in each arm. In Tanaka 2017, regardless of whether risedronate 17.5 mg/week ( or 2.5 mg/day) was used alone or combined with menatetrenone 45 mg/day, a similar RR of 1.13 (95% CI 0.55 to 2.30) was observed.

**Radiographic vertebral fractures (**Analysis 20.2**)**

One study (Sarioglu 2006) compared daily risedronate (5 mg) to weekly alendronate (70 mg) for one year. Zero radiographic vertebral fractures were inferred from the text of the paper and the RR was not estimable. Two studies comparing weekly risedronate (35 mg) with daily subcutaneous injection of teriparatide (20 µg) reported 97 of 842 risedronate-treated (11.5%) and 44 of 833 teriparatide-treated (5.3%) women sustained at least one radiographic vertebral fracture (Hadji 2012; Kendler 2018). The pooled estimate of the RR demonstrated risedronate 35 mg/mg was less effective than teriparatide 20 µg/day (RR 2.18, 95% CI 1.55 to 3.07).

When used at the daily dose of 2.5 mg, risedronate was compared to etidronate 200 mg/day (Fukunaga 2002) and monthly intravenous injection of Ibandronate 1 mg (Nakamura 2013), with the estimated RRs of 0.21 (95% CI 0.01,4.32) and 1.16 (95% CI 0.78,1.75), respectively. We were unable to reject the null hypothesis of risedronate having similar anti-fracture effects to etidronate and ibandronate. When added to menatetrenone 45 mg/day, the difference between risedronate alone and combined use was not sufficiently precise (RR 0.84, 95% CI 0.64 to 1.11) (Kasukawa 2014).

**Health-related quality of life (**Analysis 23.1**)**

Only two two-year secondary prevention studies comparing risedronate 35 mg/week with subcutaneous injection of teriparatide 20 µg reported health-related quality of life. Hadji 2012 used European Quality of Life Questionnaire (EQ-5D-5) and Kendler 2018used European Foundation for Osteoporosis Quality of Life Instrument (QUALEFFO), so standardised mean difference was used for analysis. Little or no difference between two treatments were observed (SMD -0.01, 95% CI -0.10 to 0.08).

**Gastrointestinal adverse events (**Analysis 24.2**)**

This outcome was only available for risedronate compared with other bisphosphonates. In total, 134 out of 617 (21.7% ) risedronate-treated women and 153 of 622 (24.6%) alendronate-treated women experienced gastrointestinal events with a pooled RR 0.88 (95% CI 0.72 to 1.08) (Hosking 2003; Reid 2006). Conversely, the lower dose of risedronate (2.5 mg/day) seemed to have a higher percentage of women experiencing gastrointestinal events (22.9%) when compared with the lower dose of cyclic etidronate (200 mg/day) (19.7%) [ estimated RR of 1.16 (95% CI 0.71 to 1.91)] (Fukunaga 2002). The concurrent treatment of risedronate 17.5 mg/week (or 2.5 mg/day) and menatetrenone 45 mg/day was observed to have more participants complaining of gastrointestinal adverse events (4.1%) than risedronate used alone (2.5%) (Tanaka 2017). The reported incidents in this trial were comparatively lower than those reported in other included trials, for which the rates were closer to 20% (Hosking 2003; Reid 2006; Fukunaga 2002). Nevertheless, none of the comparisons had a 95% confidence interval that would lead us to reject the null hypotheses of no difference between risedronate and other bisphosphonates.

**Atypical femoral fracture (**Analysis 25.2**)**

Zero atypical femoral fractures were reported or inferred in the trials comparing risedronate at different dose schedules versus other active agents, including alendronate 70 mg/week (Akyol 2006; Galesanu 2011; Paggiosi 2014a; Sarioglu 2006), monthly intravenous injection of ibandronate 1 mg (Nakamura 2013) or monthly oral use of ibandronate 150 mg (Galesanu 2011; Paggiosi 2014a), daily injection of teriparatide 20 µg (Kendler 2018) and bi-annual injections of denosumab 60 mg (Roux 2014).

**Acute phase reactions (**Analysis 26.1**)**

Only one three-arm trial (Paggiosi 2014a) reported this outcome. One, two and seven participants who used risedronate 35 mg/week, alendronate 70 mg/week and ibandronate 150 mg/month, respectively, experienced acute phase reactions during the two-year treatment. The estimates for RR for the comparison of risedronate with alendronate and ibandronate were 0.49 (95% CI

0.05 to 5.27) and 0.14 (95% CI 0.02 to 1.11), respectively. Both 95% confidence intervals were too wide to indicate a benefit from risedronate.

**Osteonecrosis of the jaw (**Analysis 27.1**)**

Zero incidents were reported from three trials comparing risedronate 35 mg/week versus teriparatide 20 µg/day for one year (Kendler 2018), risedronate 150 mg/month versus denosumab 60 mg/day for two years (Roux 2014), and risedronate 2.5 mg/day versus monthly intravenous injection of ibandronate 1 mg/day for three years (Nakamura 2013).

**Atrial fibrillation (**Analysis 28.1**)**

Paggiosi 2014a reported one, two and one participants in risedronate 35 mg/week, alendronate 70 mg/week and ibandronate 150 mg/month group, respectively, experienced atrial fibrillation. The estimated RRs comparing risedronate with alendronate and ibandronate were 0.49 (95% CI 0.05 to 5.27) and 0.98 (95% CI 0.06 to 15.34), respectively. In Roux 2014, zero participants on risedronate 150 mg/month and two on denosumab 60 mg/day experienced this adverse event. When compared to teriparatide 20 µg/day, weekly use of risedronate 35 mg appeared to have a 19% increased risk of developing atrial fibrillation (RR 1.19, 95% CI 0.39 to 3.69). However, none of the comparisons allowed us to reject the null hypotheses of no risk differences between risedronate and other anti-osteoporotic drugs.

# DISCUSSION

## Summary of main results

This updated review expands the scope of our PICO by including active comparison trials and providing more detailed outcome analyses. It summarises the findings from 33 studies (27,348 participants) comparing risedronate with placebo/no intervention, and other anti-osteoporotic drugs. Applying a peer-reviewed hierarchical classification based on the participant's risk of fractures, seven and 26 trials were defined as primary and secondary prevention, respectively, none of which were judged to be at low risk of bias in all seven domains.

When compared to placebo/no intervention, four primary (989 participants) and nine secondary prevention trials (14,354 participants) reported data for major outcomes. We downgraded most of the evidence to low or very low certainty due to concerns about imprecision and risk of bias. The limited evidence from primary prevention trials did not suggest any benefits or harms from the daily use of risedronate. However, for secondary prevention, risedronate 5 mg/day probably results in relative risk reductions of 20% and 27% in non-vertebral and hip fractures that are probably of clinical importance. We do not know if risedronate 5 mg/day reduces the risk for wrist fractures because the certainty of the current evidence is very low. Risedronate's effect on clinical vertebral fracture is unknown because no estimable effect was observed given the limited evidence. Risedronate probably results in a clinically important relative risk reduction of 39% in radiographic vertebral fractures. Similar effects in withdrawals due to adverse events and serious adverse effects were observed between risedronate 5 mg/day and placebo.

The lower daily dose of risedronate (2.5 mg) was less frequently investigated and most of the data were extracted from studies in which the risedronate 2.5 mg/day arm was discontinued due to protocol amendment. The limited data only demonstrated that risedronate 2.5 mg was better than placebo in the secondary prevention of radiographic vertebral fractures, with a risk reduction of 37% (RR 0.63, 95% CI 0.45 to 0.87). A difference was also observed for withdrawals due to adverse events (RR 0.89, 95% CI 0.81 to 0.98), which, however, was likely biased by the early termination of risedronate 2.5 mg/day in the relevant studies.

When we compared different daily doses of risedronate, probable differences were only observed for radiographic vertebral fractures in secondary prevention, where fewer participants treated with risedronate 5 mg/day compared to those with 2.5 mg/day sustained a fracture (RR 0.66, 95% CI 0.44 to 0.98). Although the lower daily dose was observed to reduce the risk for withdrawals due to adverse events (RR 1.43, 95% CI 1.17 to 1.74), this effect may have been biased by the early termination of risedronate 2.5 mg/day in the relevant studies. Although there was little to no difference in fracture outcomes between the therapeutically equivalent formulations of risedronate, it is worth noting that one woman from these comparison studies who was taking daily risedronate 5 mg developed osteonecrosis of the jaw. In addition, fewer participants treated with daily 5 mg compared to those with monthly 150 mg experienced acute phase reactions (RR 0.67, 95% CI 0.48 to 0.94) and serious adverse events (RR 0.11, 95% CI 0.01 to 0.89).

When compared to other osteoporotic drugs, including both bisphosphonates and non-bisphosphonates, different regimens of risedronate (daily, weekly and monthly) were also investigated. Most of the evidence comparing risedronate with active drugs for primary and secondary prevention came from single trials. Alendronate and teriparatide were the most frequent comparators. No benefits or harms were observed between risedronate and other anti-osteoporotic drugs except for two comparisons regarding withdrawals due to adverse events: weekly risedronate 35 mg versus daily PTH 1-84 100 µg (RR 0.24, 95% CI 0.07 to 0.82), and weekly risedronate 17.5 mg alone versus the combination of risedronate 17.5 mg/week and menatetrenone 45 mg/day (RR 0.63, 95% CI 0.41 to 0.98).

For the 10 studies excluded from analyses due to the lack of extractable or comparable data, reasons for exclusions were described and the results (if a pair-wise comparison was available) were summarised in Appendix 5. Based on the limited evidence, we observed that Clemmesen 1997 reported notably higher risks for the minor outcome radiographic vertebral fractures compared to those in the base case (Summary of findings 2): 29.5% risedronate-treated and 45.5% placebo-treated women (versus 10.6% and 17.3% in the base case, respectively), experienced at least one incident. The higher risks might have been due to the inclusion of a one-year no treatment period.

## Overall completeness and applicability of evidence

This review summarises findings from 43 studies conducted between 1997 and 2017. Most of the trials were multi-national (k = 17) or conducted in one country with multiple study sites (k =7). Among the 22 studies which reported race, Caucasians accounted for the majority of the included participants in four primary (95% to 100%) and 10 secondary prevention studies (79% to 100%), followed by Asians who were exclusively recruited in one primary and seven secondary prevention studies. The ranges

of the participants' baseline age (51.5 to 77.7 years old) and BMD T-scores were wide (femoral neck: 0.76 to -3.70; lumbar spine: -0.40 to -3.62). 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, we applied a hierarchical classification algorithm. It was developed through a peer-reviewed consensus process based on WHO diagnostic criteria for osteoporosis, lending it both content and face validity. Its criterion validity was directly or indirectly confirmed by the following: A) After treatments for one to three years, the risk of fractures for women receiving placebo in the secondary prevention studies was indeed higher than that of the placebo groups in primary prevention studies, i.e. clinical vertebral fractures (primary 0% versus secondary 0%, not testable); non-vertebral fractures (primary 5.1% versus secondary 10.2%; P value (two-tailed probability) = 0.0147), hip fractures (primary 0% versus secondary 3%; P value= 0.0939), wrist fractures (primary 1.1% versus secondary 2.5%; P value= 0.836) and radiographic vertebral fractures [primary 6.2% versus secondary 17.3%; P value 0.0003]. B) Two secondary and zero primary prevention studies included only participants who had previous exposure to any bisphosphonate. C) Age is the last criteria in the hierarchy, which was used only when we were unable to classify an included study with limited information for the earlier criteria. Among all included studies, four secondary (Kasukawa 2014; McClung 2001; Ohtori 2013; Tanaka 2017) and zero primary prevention studies recruited participant whose baseline mean age were 75 or greater. The categorisation 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). This helps stakeholders make decisions appropriate to the fracture risk of the targeted population.

Five fracture outcomes and other endpoints of clinical significance were assessed in this review, among which the evidence for health-related quality of life and some rare safety events relevant to bisphosphonates in the later development phase were mainly provided by the active comparison trials. Given that the evidence was separately reviewed and analysed from primary and secondary prevention trials based on participants' risk of fracture, the results independently address our research questions. A majority of the included studies (k=27, 82%) were defined as secondary prevention as they targeted postmenopausal women who had higher risk of fracture, and a greater need of anti-osteoporotic treatment. We apply a clinically important reduction of >15% in presenting the evidence for benefit outcomes. The clinical treatment decision threshold was determined by a consensus of clinical specialists and research methodologists who took into account the diversity of five fracture outcomes, and the respective baseline rates and seriousness (Wells 2008. This approach not only avoids the fallacy of P value (Dixon 2003), but is in agreement with the reporting practice recommended by Cochrane Effective Practice and Organization of Care Group (EPOC 2018): 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.

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

## Quality of the evidence

Following the GRADE approach (GRADE 2015; Schünemann 2013), we constructed summary of findings tables for risedronate 5 mg/day for both primary and secondary prevention, each including four fracture outcomes and two safety outcomes (withdrawals due to adverse events and serious adverse events). We did not detect any publication bias in our analyses since either few randomised controlled trials (RCTs) were included or the included RCTs were symmetrically distributed around the best estimate.

For primary prevention, the certainty of evidence was rated from "low" to "very low" across different outcomes. The main limiting factor leading to the decrease in certainty for all of the outcomes was "imprecision". The evidence of non-vertebral, wrist fractures and withdrawals due to adverse events and serious adverse events were all downgraded two levels for imprecision because the optimal information size was not met and the confidence interval of the effect estimates included both appreciable benefit and harm (Schünemann 2013). The evidence for clinical vertebral and hip fractures was downgraded two levels for imprecision because there were very few or zero events reported in the included studies which often had inadequate sample sizes. In addition, the certainty of the evidence for non-vertebral fractures as well as serious adverse events was further reduced by one level because most of the included studies were subject to high risk of (attrition) bias. High heterogeneity between studies ($I^2$=70 % and a non-significant test for heterogeneity P value 0.07) was only found in serious adverse events, which resulted in its evidence being downgraded one-level. For all outcomes, none of the evidence was compromised by indirectness because an explicit PICO framework was adhered to along the reviewing process.

For secondary prevention, the certainty of evidence was ranked from "high" to "very low" across different outcomes. High risk of (attrition and performance) bias was the most frequent factor that resulted in a downgrade of the evidence certainty by one level for non-vertebral, hip and wrist fractures and serious adverse events. The limiting factor "imprecision" resulted in a two-level certainty reduction for clinical vertebral and wrist fractures. "Indirectness" was an issue for two outcomes due to their inclusion of McClung 2001, in which two daily doses (5 and 2.5 mg) were used and the results were not reported separately. For non-vertebral fractures, the evidence was not downgraded because the sensitivity analysis excluding McClung 2001 (Analysis 8.2, secondary prevention) did not change the direction and precision of the effect estimate of the base case. However for hip fractures, the evidence was downgraded one level because McClung 2001 contributed most of the evidence in the base case, and its exclusion resulted in a non-estimable effect.

In summary, the certainty of evidence for risedronate 5 mg/day for secondary prevention is higher than that for primary prevention. Since the former included a larger amount of evidence, "imprecision" was observed to be the main factor accounting for the difference.

## Potential biases in the review process

To minimise the possibility of introducing bias, we followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020) and referred to the *Methodological Expectations of Cochrane Intervention*

*Reviews* (MECIR) standards (Higgins 2021) to avoid common errors. Several approaches were adopted to supplement the potential limitations along the reviewing process. We conducted Peer Review of Electronic Search Strategies (PRESS) (McGowan 2016) on a list of pre-identified databases to capture the eligible studies. We did not exclude studies on language, date and 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 (Evidence Partners, Ottawa, Canada) to ensure the independence, impartiality and inter reliability of review authors, while securely storing research materials for the future research.

However, the following biases were acknowledged. First, adherence to the hierarchical classification algorithm was dependent on the adequacy of reporting in the included studies and there were inconsistencies across the included trials as to how the level of risk is defined. For example, we required the clinical diagnosis of osteoporosis (for secondary prevention) to be supported with criteria or references in agreement with the World Health Organization (WHO 1994). If a study only mentioned "osteoporosis" in the text or recruited "osteoporotic women" without any clarification, we would not classify it as secondary prevention unless any subsequent criteria were met. Among the 33 studies included in the quantitative synthesis, one study did not meet the diagnostic criteria due to lack of supporting information (Muscoso 2004), and another (Rosen 2005) provided only a T-score of < 2 as a criterion versus WHO which requires ≤ 2.5. Both studied active treatment comparisons, however, so were not included in the base-case analysis. Second, we only included RCTs longer than one year, therefore, we might have overlooked short-term safety issues for risedronate. Nevertheless, we measured the outcomes frequently related to bisphosphonate use, including gastrointestinal adverse events, atypical femoral fractures and osteonecrosis of the jaw. The outcomes of withdrawals due to adverse events and serious adverse events were used to indirectly observe some of the intolerable events occurring within the first year of the treatment. Given that risedronate-treated participants did not have an increased risk in the occurrence of withdrawals due to adverse events and serious adverse events, the short-term safety events that might have been missed were probably tolerable and transient. Third, we aimed to collect high-quality evidence from RCTs. For studies with an extension period in which the randomly assigned treatments were no longer maintained, the outcome data were not used. For example, Clemmesen 1997 reported outcomes after a one-year no-treatment follow-up period, and in the 6-7 year extension period of Reginster 2000, all women received risedronate 5 mg/day (Mellstrom 2004). Data reported during those periods were excluded from the analyses. Fourth, the unit of measurement for dichotomous outcomes was the number of participants with the event instead of the number of events. Although the incidence conveys better information about the risk of the outcome occurrence and was more frequently reported, we did lose some data given this limitation. For example, the outcome of gastrointestinal adverse events, NCT02063854 reported the number of participants sustaining individual gastrointestinal symptoms. The individual incidents cannot be added up to form a composite outcome since any of the participants could have complained of more than one symptom. Another example was seen in Harris 1999 and Reginster 2000, which had two-year extension periods after the original three-year follow-up. The fractures reported for years four to five could not be added to the previous three-year data as it was not clear whether any of the women experienced a subsequent fracture after their first occurring in the previous three years. However, instances in which the outcome data were not usable or not extractable were relatively few and were recorded in our database. The years four to five anti-fracture data for risedronate 5 mg/day (Harris 1999;Reginster 2000) were described narratively (in "Subgroup Analysis-Different treatment durations"). Finally, there are underlying limitations in evaluating safety outcomes based on summary meta-analyses of RCTs which may include healthier participants with fewer co-morbid diseases, shorter follow-ups, lack of prespecified hypothesis and rigorous methods for harms. The evidence for safety outcomes, especially the rare adverse events that we studied may underestimate the risk of risedronate's toxicity.

### Agreements and disagreements with other studies or reviews

This update expands on the key findings from our previous Cochrane Review, in which only placebo-controlled trials of risedronate were included and analysed (Wells 2008). Most of the relevant reviews which have been conducted recently have been network meta-analyses combining direct and indirect evidence for risedronate compared to placebo or other active treatments (Barrionuevo 2019; Chandran 2019; Ellis 2014; Hopkins 2011; Jansen 2011; Liu 2018; Migliore 2013; Yang 2016; Zhou 2016). In addition to the different analytic strategies, the varied study scopes and inclusion criteria present a challenge when comparing results between reviews. A notable difference is that these reviews targeted postmenopausal women who were being treated for osteoporosis (regardless of the existence of patients' characteristics and/or guideline criteria to support this diagnosis) whereas our review differentiated the populations of postmenopausal women at different risks of fracture. This might have resulted in their omission of trials recruiting postmenopausal women who were at lower risk of fractures (e.g. some of the nine primary prevention trials were included in our review) and who were at higher risk of fracture but were not described as having a diagnosis of osteoporosis (e.g. some of the 13 secondary prevention trials which were defined by the criteria other than diagnosis in our review). In addition, some of the reviews also restricted trial inclusion on criteria such as intervention/comparator (Chandran 2019; Ellis 2014), reported outcomes (Ellis 2014; Hopkins 2011; Liu 2018; Migliore 2013; Yang 2016; Zhou 2016), double-blinding (Migliore 2013), study duration (Migliore 2013), published form or language (i.e. full-published, in English) (Ellis 2014; Jansen 2011; Liu 2018; Migliore 2013; Zhou 2016), sample size of the study (Yang 2016), or study quality (Chandran 2019). Whereas we differentiate radiographic versus clinical vertebral based on the outcome definitions provided in each included studies, the other reviews appeared to have analysed the two outcomes together. Our review updating the direct comparison evidence for risedronate, included the largest number of RCTs given that our only study restriction was follow-up greater than one year. Hopkins 2011, for example, the only review which targeted all postmenopausal women as we did, limited the inclusion criteria on reported outcomes (fractures as a primary or secondary outcome) and comparators (placebo controlled trials). From a search up to 2009, it included six out of the 23 eligible studies reporting fracture outcomes in our review (two out of six primary and four of 17 secondary prevention studies). Its reported benefits for risedronate were similar to our secondary prevention results. When

compared to placebo, benefits were observed for vertebral, non-vertebral, and hip fractures, with the estimates for odds ratios (OR) of 0.59 [95% credible interval (CrI) 0.47 to 0.75)], 0.79 (95% CrI 0.69 to 0.89), and 0.74 (95% CrI 0.58 to 0.94), respectively. When compared to other anti-osteoporotic drugs, including alendronate, etidronate, ibandronate and raloxifene, via indirect comparisons, risedronate showed little or no difference in reducing fracture risk. All reported results were similar to ours in terms of the direction, magnitude and precision of the estimates. Barrionuevo 2019, targeting postmenopausal women with osteoporosis or osteopenia and limiting inclusion criteria on fracture outcomes, provided direct comparisons of risedronate versus placebo for vertebral (0.64, 95% CI 0.53 to 0.77), non-vertebral (0.86, 95% CI 0.72 to 0.89), and hip fractures (0.74, 95% CI 0.59 to 0.94), which were similar to our results and appeared to be based on the combined evidence of our primary and secondary prevention studies for non-vertebral (0.80, 95% CI 0.71 to 0.89), hip fractures (0.73, 95% CI 0.56 to 0.94), and radiographic vertebral (0.63, 95% CI 0.51 to 0.77). However, the differences they found between risedronate and ibandronate for non-vertebral (0.73, 95% CI 0.56 to 0.97), and between risedronate and abaloparatide for non-vertebral (4.32, 95% CI 1.44 to 12.99) were not observable in our pair-wise analysis.

From a safety perspective, risedronate was observed to make little or no difference compared to placebo and other anti-osteoporotic drugs, for any adverse event. The only two exceptions were that fewer women who received weekly risedronate 35 mg than those who used daily PTH 1-84 100 µg, and fewer women on weekly risedronate 17.5 mg alone than those receiving risedronate 17.5 mg/week plus menatetrenone 45 mg/day withdrew from the study because of adverse events. This safety profile of risedronate was largely in tune with the results from other relevant reviews. Tadrous 2014, for example, conducted a systematic review of blinded RCTs that assessed bisphosphonates for osteoporosis through to 2012. No difference was found between risedronate and placebo in withdrawals due to adverse events and gastrointestinal adverse events. Furthermore, risedronate had the lowest probability of having the highest number of adverse events compared to other bisphosphonates including alendronate, etidronate and zoledronic acid.

In our review, we could not infer a causal relationship between risedronate exposure and osteonecrosis of the jaw given that only one woman experienced this event. The case description was similar to that observed in (Mavrokokki 2007) in which the condition occurred after dental extraction and responded to dental treatment. The higher risk (of osteonecrosis) observed for bisphosphonates (OR 2.32; 95 % CI 1.38 to 3.91) in a systematic review (Lee 2014) of 12 observational studies may have limited applicability to our results since it targeted a wide range of indications and involved different uses and forms of bisphosphonates. The rarity of this serious adverse event [between 0.02% and 0.06% as estimated for osteoporosis patients with long-term use of bisphosphonates (Lee 2014)], however, was affirmed in our review.

No women in our included studies were found to have sustained an atypical femoral fracture. A case-control study (Meier 2012) observed an increased risk of atypical femoral fracture in bisphosphonate users, with an adjusted OR 69.1 (95% CI 22.8 to 209.5). Among all investigated bisphosphonates (alendronate, risedronate, pamidronate, ibandronate, etidronate, or zoledronic acid), risedronate had the lowest estimate for the OR (5.7, 95% CI 22.8 to 209.5) and little or no difference was reported. In addition with the low incidence rate of atypical femoral fracture (32 cases per million person-years), the use of risedronate appeared to be safe with respect to this outcome.

The higher risk of atrial fibrillation attributable to oral bisphosphonates (RR 1.22, 95% CI 1.14 to 1.31) (Sharma 2014) was not observed in our review. And again, given the limited evidence, we were not able to clearly demonstrate the relationship of risedronate and acute phase reaction which is generally assumed to be caused by intravenous aminobisphosphonates (Olson 2007).

## AUTHORS' CONCLUSIONS

### Implications for practice

The prevention of osteoporotic fractures is an important public health intervention due to their association with mortality and morbidity. The optimal strategy for preventing osteoporotic fractures should be in accord with a postmenopausal women'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.

In this review, we observed that risedronate at a daily dose of 5 mg, has different benefits and harms for postmenopausal women at lower and higher risk of fractures. For the former (primary prevention), the benefit and harms of risedronate were supported by limited evidence with high uncertainty, while for the latter (secondary prevention), it probably prevents non-vertebral fractures, may reduce the risk of hip fractures, and probably does not increase serious adverse events. We are uncertain on the effects on clinical vertebral and wrist fractures. Knowing this, clinicians can make treatment decisions based on an individual patient's risk determined from her medical history (including fragility fracture) and/or BMD T-score, both of which could be easily collected in the clinical setting. Although it appears safe for postmenopausal women, the evidence for starting risedronate may not be convincing for those at lower risk of fractures. However, for women at higher risk, risedronate provides a good option. Given the current evidence, clinicians can balance the benefits and risks of anti-osteoporotic care while incorporating the patient's values and preferences. For other stakeholders including policy makers and the relevant pharmaceutical industry, effective communication applying the evidence for different levels of risk can also improve the allocation of health resources.

### Implications for research

The findings of our updated review provide a number of implications for future research. It was suggested that risedronate has greater effects in reducing non-vertebral, hip, and radiographical vertebral fractures for postmenopausal women at higher risk of fractures than placebo. However given the limited evidence, the existing data have not fully resolved the question as to whether there are important differences in risk reduction across groups of patients with varying degrees of osteoporosis, for example patients with "osteoporosis" (BMD ≥ 2.5 SD below the normal mean for young-adult women) versus patients with "severe or established osteoporosis" (BMD ≥2.5 SD in a patient who has already experienced ≥ 1 fractures), or patients experiencing fractures while receiving approved osteoporosis therapy (AACE

guidelines 2020). For primary prevention in which the anti-fracture effects of risedronate have not been demonstrated due to limited evidence, additional research is needed to clarify the role of risedronate and its impact on the early prevention of osteoporotic fractures.

Since the relevant guidelines have recommended the use of risedronate in the treatment of osteoporosis, future research should focus on generating high-quality evidence with longer follow-ups, to determine the optimal treatment duration to maximise the benefits of risedronate while avoiding the potential harms. 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 urgently needed as risedronate is one of the first-line treatments for osteoporosis and the exposed population is growing. Certainly, the quality of the relevant trials could be refined with evolving research methodologies, including larger sample sizes, better study designs, and approaches to handling and reporting bias.

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# REFERENCES

## References to studies included in this review

**Akyol 2006** *{published data only}*

Akyol Y, Tander B, Alayli G, Durmus D, Bek Y, Canturk F, et al. The comparison of effectiveness of alendronate and risedronate in osteoporosis treatment [Osteoporoz Tedavisinde Alendronat ve Risedronatin Etkinliklerinin Karsilastirilmasi (Turkish)]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi 2006;**52**:110-4.

**Anastasilakis 2008a** *{published data only}*

Anastasilakis AD, Goulis D, Polyzos SA, Gerou S, Koukoulis GN, Efstathiadou Z, et al. Head-to-head comparison of risedronate vs. teriparatide on bone turnover markers in women with postmenopausal osteoporosis: a randomised trial. *International Journal of Clinical Practice* 2008;**62**(6):919-24.

**Atmaca 2006** *{published data only}*

Atmaca A, Gedik O. Effects of alendronate and risedronate on bone mineral density and bone turnover markers in late postmenopausal women with osteoporosis. *Advances in Therapy* 2006;**23**(6):842-53.

**Bala 2014** *{published data only}*

Bala Y, Chapurlat R, Cheung A M, Felsenberg D, LaRoche M, Morris E, et al. Risedronate slows or partly reverses cortical and trabecular microarchitectural deterioration in postmenopausal women. *Journal of Bone and Mineral Research* 2014;**29**(2):380-8.

**Brown 2002** *{published data only}*

* Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcified Tissue International* 2002;**71**:103-11.

Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. *Current Medical Research and Opinion* 2004;**20**:757-64.

**Clemmesen 1997** *{published data only}*

Clemmesen B. A 2-Year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausaloOsteoporosis. *Osteoporosis International* 1997;**7**:488-95.

**Delmas 2008a** *{published data only}*

* Delmas PD, McClung MR, Zanchetta JR, Racewicz A, Roux C, Benhamou CL, et al. Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. *Bone* 2008;**42**:36-42.

McClung MR, Zanchetta JR, Racewicz A, Roux C, Benhamou CL, Man Z et al. Efficacy and safety of risedronate 150-mg once a month in the treatment of postmenopausal osteoporosis: 2-year data. *Osteoporosis International* 2013;**24**(1):293-9.

NCT00247273. A Study of Monthly Risedronate for Osteoporosis [A Phase III, Multicenter, Double-blind, Randomized, Active-controlled, Parallel Group, Non-inferiority Study Comparing 150 mg Risedronate Monthly With 5 mg Risedronate Daily in the Treatment of Postmenopausal Osteoporosis (PMO)]. ClinicalTrials.gov Database. Provided by Warner Chilcott. June 21, 2011.

**Delmas 2008b** *{published data only}*

* Delmas PD, Benhamou CL, Man Z, Tlustochowicz W, Matzkin E, Eusebio R, et al. Monthly dosing of 75 mg risedronate on 2 consecutive days a month: efficacy and safety results. *Osteoporosis International* 2008;**19**:1039-45.

McClung MR, Benhamou CL, Man Z, Tlustochowicz W, Zanchetta JR, Eusebio R, et al. A novel monthly dosing regimen of risedronate for the treatment of postmenopausal osteoporosis: 2-year data. *Calcified Tissue International* 2013;**92**(1):59-67.

**Dobnig 2006** *{published data only}*

Dobnig H, Hofbauer LC, Viereck V, Obermayer-Pietsch B, Fahrleitner-Pammer A. Changes in the RANK ligand/osteoprotegerin system are correlated to changes in bone mineral density in bisphosphonate-treated osteoporotic patients. *Osteoporosis International* 2006;**17**:693-703.

**Dundar 2009** *{published data only}*

Dundar U, Kavuncu V, Ciftci IH, Evcik D, Solak O, Cakir T. The effect of risedronate treatment on serum cytokines in postmenopausal osteoporosis: a 6-month randomized and controlled study. *Journal of Bone and Mineral Metabolism* 2009;**27**(4):464-70.

**Fogelman 2000** *{published data only}*

Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. *Journal of Clinical Endocrinology & Metabolism* 2000;**85**(5):1895-900.

**Fukunaga 2002** *{published data only}*

Fukunaga M, Kushida K, Kishimoto H, Shiraki M, Taketani Y, Minaguchi H, et al. A Comparison of the effect of risedronate and etidronate on lumbar bone mineral density in Japanese patients with osteoporosis: a randomized controlled trial. *Osteoporosis International* 2002;**13**:971-9.

**Galesanu 2011** *{published data only}*

Galesanu C, Lisnic N, Mocanu V, Florescu A, Loghin A-I, Galesanu M-R. Efficacy of bisphosphonates in the treatment of postmenopausal osteoporosis. *Osteoporosis International* 2011;**22**(Suppl 5):S739.

**Gu 2015** *{published data only}*

Gu JM, Wang L, Lin H, Chen DC, Tang H, Jin XL, et al. The efficacy and safety of weekly 35-mg risedronate dosing regimen for Chinese postmenopausal women with osteoporosis or osteopenia: 1-year data. *Chung Kuo Yao Li Hsueh Pao* 2015;**36**:841-6.

**Hadji 2012** *{published data only}*

* Hadji P, Zanchetta JR, Russo L, Recknor CP, Saag KG, McKiernan FE, et al. The effect of teriparatide compared with

risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporosis International* 2012;**23**(8):2141-50.

NCT00343252. Effect of teriparatide compared to risedronate on back pain in women with a spine fracture caused by osteoporosis [The effect of teriparatide compared with risedronate on back pain in postmenopausal women with osteoporotic vertebral fractures]. ClinicalTrials.gov Database. Provided by Eli Lilly and Company. July 12, 2010.

**Harris 1999** *{published data only}*

* Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 1999;**282**(14):1344-52.

Ste-Marie L G, Sod E, Johnson T, Chines A. Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. *Calcified Tissue International* 2004;**75**:469-76.

**Harris 2001** *{published data only}*

Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett JA Jr, Baylink DJ, et al. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. *Journal of Clinical Endocrinology & Metabolism* 2001;**86**(5):1890-7.

**Hooper 2005** *{published data only}*

Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. *Climacteric* 2005;**8**:251-62.

**Hosking 2003** *{published data only}*

Hosking D, Adami S, Felsenberg D, Andia JC, Valimaki M, Benhamou L, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. *Current Medical Research and Opinion* 2003;**19**(5):383-94.

**Kasukawa 2014** *{published data only}*

Kasukawa Y, Miyakoshi N, Ebina T, Aizawa T, Hongo M, Nozaka K, et al. Effects of risedronate alone or combined with vitamin K2 on serum undercarboxylated osteocalcin and osteocalcin levels in postmenopausal osteoporosis. *Journal of Bone and Mineral Metabolism* 2014;**32**:290-7.

**Kato 2010** *{published data only}*

Kato M, Takaishi H, Matsuzaki, H Kaneko K, Matsumoto M, Toyama Y, et al. Therapeutic effects of alfacalcidol, risedronate, and raloxifene on three-dimensional trabecular microarchitecture of cranial vertebral endplate in postmenopausal women: a prospective randomized trial using a multi-detector-raw CT imaging (SP28). In: Spine. 2010:10.

**Kendler 2018** *{published data only}*

Body JJ, Marin F, Kendler DL, Zerbini CA, López-Romero P, Möricke R. Efficacy of teriparatide compared with risedronate on FRAX® -defined major osteoporotic fractures: results of the VERO clinical trial. *Osteoporosis International* 2020;**31**:1935-42.

* Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2018;**391**:230-40.

NCT01709110. VERtebral fracture treatment comparisons in osteoporotic women (VERO) [Teriparatide and risedronate in the treatment of patients with severe postmenopausal osteoporosis: comparative effects on vertebral fractures]. ClinicalTrials.gov Database, provided by Eli Lilly and Company. January 23, 2018.

**Leung 2005** *{published data only}*

Leung JY, Ho AY, Ip TP, Lee G, Kung AW, Leung JYY, et al. The efficacy and tolerability of risedronate on bone mineral density and bone turnover markers in osteoporotic Chinese women: a randomized placebo-controlled study. *Bone* 2005;**36**(2):358-64. [MEDLINE: 274]

**Li 2005** *{published data only}*

Li Y, Zhang Z, Deng X, Chen L, Li Y, Zhang Z, et al. Efficacy and safety of risedronate sodium in treatment of postmenopausal osteoporosis. *Journal of Huazhong University of Science and Technology* 2005;**25**(5):527-9. [MEDLINE: 292]

**Lim 2017** *{published data only}*

Lim S J, Kim K, Park YS. Effect of osteoporosis medications on refracture and mortality following hip fracture surgery in postmenopausal women: a prospective randomized trial. *Osteoporosis International* 2017;**28**(1 Supplement):S250.

**McClung 2001** *{published data only}*

McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group.. *New England Journal of Medicine* 2001;**344**(5):333-40.

**McClung 2012** *{published data only}*

McClung MR, Balske A, Burgio DE, Wenderoth D, Recker RR. Treatment of postmenopausal osteoporosis with delayed-release risedronate 35 mg weekly for 2 years. *Osteoporosis International* 2013;**24**(1):301-10.

* McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, et al. Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet. *Osteoporosis International* 2012;**23**:267-76.

NCT00541658. A study of a 35 mg delayed release Formulation of Risedronate for Osteoporosis [A Non-inferiority Comparison of 35 mg delayed-release risedronate, given once-weekly either before or after breakfast, & 5 mg immediate-release risedronate, given once-daily before breakfast, in the treatment of postmenopausal osteoporosis]. ClinicalTrial.gov Database, provided by Warner Chilcott. June 21, 2011.

**Mortensen 1998** *{published data only}*

Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *Journal of Clinical Endocrinology & Metabolism* 1998;**83**(2):396-402.

**Muscoso 2004** *{published data only}*

Muscoso E, Puglisi N, Mamazza C, Lo Giudice M, Testai M, Abbate S, et al. Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. *European Review for Medical and Pharmacological Sciences* 2004;**9**:97-102.

**Nakamura 2013** *{published data only}*

Nakamura Y, Nakano T, Masako Ito M, Hagino H, Hashimoto J, Tobinai M, et al. Clinical efficacy on fracture risk and Safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis. *Calcified Tissue International* 2013;**93**:137-46.

**Narula 2012** *{published data only}*

Narula R, Mujtaba T, Iraqi AA, Singh S. Effect of risedronate and strontium therapy on bone mineral density in postmenopausal osteoporosis. *International Journal of Research in Ayurveda and Pharmacy* 2012;**3**(4):543-7.

**NCT00365456** *{published data only}*

NCT00365456. Sequential treatment of postmenopausal women with primary osteoporosis(FP-001-IM) (PEAK) [An open label, international, multi centre, parallel group, phase iii b, randomised trial, investigating lumbar spine bone mineral density (BMD) changes in postmenopausal women with primary osteoporosis initially treated with 12 months of full length parathyroid hormone (PTH 1-84) followed by 12 months of treatment with risedronate followed by either 12 months]. clinicaltrials.gov/ct2/show/NCT00365456 (first received 20 July 2012).

**NCT02063854** *{published data only}*

NCT02063854. A phase II/III, double-blind, parallel group comparative study of oral administration of NE-58095 tablets [A phase 2/3, multicenter, randomized, double-blind, parallel group comparative study to evaluate the efficacy and safety of once-monthly oral administration of NE-58095DR Tablet (25 mg or 37.5 mg) versus once-daily oral administration of NE-58095IR tablet (2.5 mg) for the treatment of involutional osteoporosis]. clinicaltrials.gov/ct2/show/NCT02063854 (first received 23 February 2017).

**Ohtori 2013** *{published data only}*

Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. Comparison of teriparatide and bisphosphonate treatment to reduce pedicle screw loosening after lumbar spinal fusion surgery in postmenopausal women with osteoporosis from a bone quality perspective. *Spine* 2013;**38**(8):E487-92.

**Paggiosi 2014a** *{published data only}*

Paggiosi M A, Peel N, McCloskey E, Walsh JS, Eastell R. Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study. *Osteoporosis International* 2014;**25**(12):2729-41.

**Reginster 2000** *{published data only}*

* Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporosis International* 2000;**11**(1):83-91.

Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003;**32**(2):120-6.

**Reid 2006** *{published data only}*

Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, Marques-Neto JF, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-Month results from FACTS-International. *International Journal of Clinical Practice* 2008;**62**(4):575-84.

* Reid D M, Hosking D, Kendler D, Brandi M L, Wark J D, Weryha G, et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: Results of FACTS 1 - International. *Clinical Drug Investigation* 2006;**26**(2):63-74.

**Rosen 2005** *{published data only}*

Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SA, et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. *Journal of Clinical Endocrinology and Metabolism* 2006;**91**(7):2631-7.

* Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *Journal of Bone and Mineral Research* 2005;**20**(1):141-51.

**Roux 2014** *{published data only}*

NCT00919711. Study to evaluate the safety and efficacy of denosumab and Actonel® in post menopausal women transitioned from alendronate therapy [A randomized open-label study to evaluate the safety and efficacy of denosumab and monthly Actonel® therapies in postmenopausal women transitioned from weekly or daily alendronate therapy]. ClinicalTrials.gov Database, provided by Amgen. December 12, 2012.

* Roux CHofbauer LC, Ho PR, Wark J D, Zillikens MC, Fahrleitner-Pammer A, et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. *Bone* 2014;**58**:48-54.

**Sarioglu 2006** *{published data only}*

Sarioglu M, Tuzun C, Unlu Z, Tikiz C, Taneli F, Uyanik BS. Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers in

postmenopausal osteoporosis. *Rheumatology international* 2006;**26**:195-200.

**Tanaka 2017** *{published data only}*

Tanaka S, Miyazaki T, Uemura Y, Miyakawa N, Gorai I, Nakamura T, et al. Comparison of concurrent treatment with vitamin K 2 and risedronate compared with treatment with risedronate alone in patients with osteoporosis: Japanese Osteoporosis Intervention Trial-03. *Journal of Bone and Mineral Metabolism* 2017;**35**(4):385-95.

**Välimäki 2007** *{published data only}*

Välimäki MJ, Farrerons-Minguella J, Halse J, Kröger H, Maroni M, Mulder H, et al. Effects of risedronate 5 mg/d on bone mineral density and bone turnover markers in late-postmenopausal women with osteopenia: a multinational, 24-month, randomized, double-blind, placebo-controlled, parallel-group, phase III trial. *Clinical Therapeutics* 2007;**29**(9):1937-49.

**Yanik 2008** *{published data only}*

Yanik B, Bavbek N, Yangk T, Inegol I, Kanbay M, Turgut FH, et al. The effect of alendronate, risedronate, and raloxifene on renal functions, based on the Cockcroft and Gault method, in postmenopausal women. *Renal Failure* 2007;**29**:471-6.

* Yanik B, Kulcu DG. The effect of raloxifene, alendronate and risedronate on serum lipid profile in postmenopausal women. *Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi* 2008;**54**(1):4-7.

## References to studies excluded from this review

**Adachi 2001** *{published data only}*

Adachi JD, Adami S, Miller PD, Olszynski W P, Kendler DL, Silverman SL, et al. Tolerability of risedronate in postmenopausal women intolerant of alendronate. *Aging - Clinical and Experimental Research* 2001;**13**:347-54.

**Altintas 2007** *{published data only}*

Altintas F, Ozkut AT, Beyzadeoglu T, Eren A, Guven M. The effect of risedronate treatment on bone turnover markers in patients with hip fracture. *Acta orthopaedica et traumatologica turcica* 2007;**41**:132-5.

**Anastasilakis 2008b** *{published data only}*

Anastasilakis AD, Goulis D G, Polyzos S A, Gerou S, Koukoulis G, Kita M, et al. Serum osteoprotegerin and RANKL are not specifically altered in women with postmenopausal osteoporosis treated with teriparatide or risedronate: a randomized, controlled trial. *Hormone and Metabolic Research* 2008;**40**(4):281-5.

**Article in Dutch 2001** *{published data only}*

No authors listed Publication in Dutch. Risedronate in the treatment and prevention of postmenopausal osteoporosis [Risedronaat, behandeling en preventie van postmenopauzale osteoporose]. *Geneesmiddelenbulletin Medische Bulletin Hulpmiddelen* 2001;**35**(9):102-3.

**Bahlous 2009** *{published data only}*

Bahlous A, Bouzid K, Sahli H, Sallami S, Abdelmoula J. Effects of risedronate on bone turnover markers in osteoporotic postmenopausal women: comparison of two protocols of treatment. *Tunisie Medicale* 2009;**87**:380-1.

**Bala 2013** *{published data only}*

Bala Y, Chapurlat R, Felsenberg D, Thomas T, LaRoche M, Morris E, et al. Risedronate slows or partly reverses microarchitecture deterioration depending on whether remodelling is perturbed or in steady state. *Osteoporosis International* 2013;**24**:S58-59.

**Borah 2004** *{published data only}*

Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. *Bone* 2004;**34**:736-46.

**Borah 2005** *{published data only}*

Borah B, Ritman EL, Dufresne TE, Borah B, Ritman EL, Dufresne TE, et al. The effect of risedronate on bone mineralization as measured by micro-computed tomography with synchrotron radiation: correlation to histomorphometric indices of turnover. *Bone* 2005;**37**:1-9.

**Borah 2010** *{published data only}*

Borah B, Dufresne T, Nurre J, Phipps R, Chmielewski P, Wagner L, et al. Risedronate reduces intracortical porosity in women with osteoporosis. Journal of Bone and Mineral Research 2010;**25**:41-7.

**Borah 2010a** *{published data only}*

Borah B, Dufresne T, Nurre J, Chmielewski P, Phipps R, McCullough L, et al. Risedronate reduces intracortical porosity in postmenopausal women with osteoporosis as measured by a new 3D Micro-CT method. *Bone* 2010;**46**:S61.

**Brown 2014** *{published data only}*

Brown JP, Roux C, Ho PR, Bolognese MA, Hall J, Bone HG, et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bisphosphonate. *Osteoporosis International* 2014;**25**:1953-61.

**Caffarelli 2010** *{published data only}*

Caffarelli C, Gonnelli S, Tanzilli L, Martini G, Nuti R. Apparent bone mineral density at femoral neck in the monitoring the early effects of teriparatide. *Bone* 2010;**47**:S203-4.

**Carlino 2011** *{published data only}*

Carlino G, Cozzolongo A. Effects of intravenous zoledronic acid following subcutaneous teriparatide in postmenopausal osteoporosis. *Bone* 2011;**48**:S220.

**Chapurlat 2011** *{published data only}*

Chapurlat R, Seeman E. Risedronate reduces cortical structural decay during menopause, probably by reducing intracortical porosity. *Osteoporosis International* 2011;**22**(Suppl 1):S100.

**Chung 2009** *{published data only}*

Chung YS, Lim SK, Chung HY, Lee I K, Park IH, Kim GS, et al. Comparison of monthly ibandronate versus weekly risedronate in preference, convenience, and bone turnover markers in Korean postmenopausal osteoporotic women. *Calcified Tissue International* 2009;**85**:389-97.

**D'Amelio 2008** *{published data only}*

D'Amelio P, Grimaldi A, Di Bella S, Tamone C, Brianza SZ, Ravazzoli MG, et al. Risedronate reduces osteoclast precursors and cytokine production in postmenopausal osteoporotic women. *Journal of Bone and Mineral Research* 2008;**23**:373-9.

**Dane 2008** *{published data only}*

Dane C, Dane B, Cetin A, Erginbas M. Effect of risedronate on biochemical marker of bone resorption in postmenopausal women with osteoporosis or osteopenia. *Gynecological Endocrinology* 2008;**24**:207-13.

**Delmas 2007** *{published data only}*

Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. *Journal of clinical endocrinology and metabolism* 2007;**92**:1296-304.

**Dufresne 2003** *{published data only}*

Dufresne TE, Chmielewski PA, Manhart M, D, Johnson TD, Borah B, et al. Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional microcomputed tomography. *Calcified Tissue International* 2003;**73**:423-32.

**Duque 2009** *{published data only}*

Duque G, Li W, Adams M, Xu S, Phipps R. Effects of risedronate on bone marrow adipocytes in postmenopausal women. *Bone* 2009;**44**(Suppl 1):S53.

**Duque 2011** *{published data only}*

Duque G, Li W, Adams M, Xu S, Phipps R. Effects of risedronate on bone marrow adipocytes in postmenopausal women. *Osteoporosis International* 2011;**22**:1547-53.

**Durchschlag 2006** *{published data only}*

Durchschlag E, Paschalis EP, Zoehrer R, Roschger P, Fratzl P, Recker R, et al. Bone material properties in trabecular bone from human iliac crest biopsies after 3- and 5-year treatment with risedronate. *Journal of Bone and Mineral Research* 2006;**21**:1581-90.

**Eastell 2003** *{published data only}*

Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *Journal of Bone and Mineral Research* 2003;**18**:1051-6.

**Eastell 2010** *{published data only}*

Eastell R, Vrijens B, Cahall D, Roux C, Ringe J, Garnero P, et al. Relationships between osteoporosis medication adherence, surrogate marker outcomes and non-vertebral fracture incidence. *Bone* 2010;**47**:S200-1.

**Eastell 2011** *{published data only}*

Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB. Bone turnover markers and bone mineral density response with risedronate therapy: relationship with fracture risk and patient adherence. *Journal of Bone and Mineral Research* 2011;**26**:1662-9.

**Eastell 2013** *{published data only}*

Eastell R, Paggiosi M, Peel N, McCloskey E, Walsh J. The effects of oral bisphosphonate therapy on the peripheral skeleton in postmenopausal osteoporosis: The trio study. *Journal of Bone and Mineral Research* 2013;**28**(S1):Available at https://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=51d4e88b-f79d-47e2-a15b-134f0c57b52e. Accessed July 08, 2020.

**Eriksen 2002** *{published data only}*

Eriksen EF, Melsen F, Sod E, Barton I, Chines A. Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. *Bone* 2002;**31**(5):620-5.

**Fujita 2009** *{published data only}*

Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y. Comparison of the analgesic effects of bisphosphonates: etidronate, alendronate and risedronate by electroalgometry utilizing the fall of skin impedance. *Journal of Bone and Mineral Metabolism* 2009;**27**:234-9.

**Geusens 2017** *{published data only}*

Geusens P, Marin F, Kendler L, Russo L, Zerbini CA, Greenspan S, et al. Teriparatide compared with risedronate and the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: The VERO Trial. *Journal of Bone and Mineral Research* 2017;**32**(Supplement 1):S22.

**Goa 1998** *{published data only}*

Goa KL, Balfour JA. Risedronate. *Drugs and Aging* 1998;**13**:83-92.

**Gonnelli 2006** *{published data only}*

Gonnelli S, Martini G, Caffarelli C, Salvadori S, Cadirni A, Montagnani A, et al. Teriparatide's effects on quantitative ultrasound parameters and bone density in women with established osteoporosis. *Osteoporosis International* 2006;**17**:1524-31.

**Gossiel 2010** *{published data only}*

Gossiel F, Hannon R, Eastell R. The effect of 3 orally-administered bisphosphonates on the resorption of type I collagen in postmenopausal osteoporosis. *Bone* 2010;**47**:S204.

**Gossiel 2016** *{published data only}*

Gossiel F, Hoyle C, McCloskey EV, Naylor KE, Walsh J, Peel N. The effect of bisphosphonate treatment on osteoclast precursor cells in postmenopausal osteoporosis: The TRIO study. *Bone* 2016;**92**:94-9.

**Gossiel 2018** *{published data only}*

Gossiel F, Paggiosi M, Naylor K, McCloskey E, Walsh J, Peel N, et al. The effect of bisphosphonates on bone turnover and bone balance in postmenopausal women with osteoporosis: The

T-score bone marker approach in the trio study. *Osteoporosis International* 2018;**29**(Supplement 2):S621-2.

**Hadji 2011** *{published data only}*

Hadji P, Dalsky GP. Effect of teriparatide compared with risedronate on reduction of back pain and new vertebral fractures in postmenopausal women with osteoporotic vertebral fractures. *Bone* 2011;**48**:S228.

**Hadji 2011a** *{published data only}*

Hadji P, Zanchetta JR, Russo LA, Recknor CP, Saag KG, Mckiernan FE, et al. Effect of teriparatide compared with risedronate on back pain and incident vertebral fractures in postmenopausal women with osteoporotic vertebral fractures. *Bone* 2011;**48**:S82.

**Hagino 2014** *{published data only}*

Hagino H, Yoshida S, Hashimoto J, Matsunaga M, Tobinai M, Nakamura T. Increased bone mineral density with monthly intravenous ibandronate contributes to fracture risk reduction in patients with primary osteoporosis: three-year analysis of the MOVER study. *Calcified Tissue International* 2014;**95**(6):557-63.

**Harris 1999a** *{published data only}*

Harris ST, Wasnich R, Ettinger M, Davidson M, Bosch L, Chines A. The effects of risedronate plus estrogen compared with estrogen alone in postmenopausal women. *Journal of Bone and Mineral Research* 1999;**14**(Suppl 1):S404.

**Hofbauer 2013** *{published data only}*

Hofbauer LC, Fahrleitnerpammer A, Ho PR, Hawkins F, Roux C, Micaelo M, et al. Efficacy and safety of denosumab vs. Risedronate in postmenopausal women suboptimally adherent to alendronate: Results from a randomized open-label study. *Osteoporosis International* 2013;**24**(1 Suppl 1):S218-S219.

**Hongo 2015** *{published data only}*

Hongo M, Miyakoshi N, Kasukawa Y, Ishikawa Y, Shimada Y. Additive effect of elcatonin to risedronate for chronic back pain and quality of life in postmenopausal women with osteoporosis: a randomized controlled trial. *Journal of Bone and Mineral Metabolism* 2015;**33**:432-9.

**Hooper 1999** *{published data only}*

Hooper M, Ebeling P, Roberts A. Risedronate prevents bone loss in early postmenopausal women. *Calcified Tissue International* 1999;**64**:80.

**Hosking 2009** *{published data only}*

Hosking D, Brandi M, Diaz-Curiel M, Felsenberg D, Hyldstrup LH. One year of treatment with PTH (1-84) and the change in lumbar spine BMD in postmenopausal women with primary osteoporosis after pre-treatment with a bisphosphonate. *Bone* 2009;**44**:S428.

**Iizuka 2008** *{published data only}*

Iizuka T, Matsukawa M. Potential excessive suppression of bone turnover with long-term oral bisphosphonate therapy in postmenopausal osteoporotic patients. *Climacteric* 2008;**11**:287-95.

**Ilter 2006** *{published data only}*

Ilter E, Karalok H, Tufekci EC, Batur O. Efficacy and acceptability of risedronate 5 mg daily compared with 35 mg once weekly for the treatment of postmenopausal osteoporosis. *Climacteric* 2006;**9**:129-34.

**Imai 2017** *{published data only}*

Imai T, Tanaka S, Kawakami K, Miyazaki T, Hagino H, Shiraki M, et al. Health state utility values and patient-reported outcomes before and after vertebral and non-vertebral fractures in an osteoporosis clinical trial. *Osteoporosis International* 2017;**28**(6):1893-901.

**Iwamoto 2016** *{published data only}*

Iwamoto J, Okano H, Furuya T, Urano T, Hasegawa M, Hirabayashi H, et al. Patient preference for monthly bisphosphonate versus weekly bisphosphonate in a cluster-randomized, open-label, crossover trial: Minodroate Alendronate/Risedronate Trial in Osteoporosis (MARTO). *Journal of Bone and Mineral Metabolism* 2016;**34**:201-8.

**Kanis 2005** *{published data only}*

Kanis J A, Barton I P, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. *Osteoporosis International* 2005;**16**:475-82.

**Karadag-Saygi 2011** *{published data only}*

Karadag-Saygi E, Akyuz G, Bizargity P, Ay P. The effect of risedronate treatment on serum osteoprotegerin and bone marker levels in postmenopausal women with osteoporosis. *Gynecological Endocrinology* 2011;**27**:1033-6.

**Kendler 2009** *{published data only}*

Kendler DL, Ringe JD, Ste-Marie L G, Vrijens B, Taylor E B, Delmas PD. Risedronate dosing before breakfast compared with dosing later in the day in women with postmenopausal osteoporosis. *Osteoporosis International* 2009;**20**:1895-902.

**Kendler 2017** *{published data only}*

Kendler DL, Zerbini C, Russo L, Greenspan S, Zikan V, Bagur A, et al. Effects of 24 months treatment of teriparatide compared with risedronate on new fractures in postmenopausal women with severe osteoporosis: a randomized, double-dummy, clinical trial. *Osteoporosis International* 2017;**28**(Suppl 1):S69-70.

**Kushida 2004** *{published data only}*

Kushida K, Fukunaga M, Kishimoto H, Shiraki M, Itabashi A, Inoue T, et al. A comparison of incidences of vertebral fracture in Japanese patients with involutional osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. *Journal of Bone and Mineral Metabolism* 2004;**22**:469-78.

**Lanza 2000** *{published data only}*

Lanza FL, Hunt RH, Thomson A BR, Provenza JM, Blank MA. Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. *Gastroenterology* 2000;**119**:631-8.

**Lanza 2000a** *{published data only}*

Lanza FL, Rack MF, Li Z, Krajewski SA, Blank MA. Placebo-controlled, randomized, evaluator-blinded endoscopy study of risedronate vs. aspirin in healthy postmenopausal women. *Alimentary Pharmacology and Therapeutics* 2000;**14**:1663-70.

**Licata 1997** *{published data only}*

Licata AA. Bisphosphonate therapy. *American Journal of the Medical Sciences* 1997;**313**(1):17-22.

**Masud 2009** *{published data only}*

Masud T, McClung M, Geusens P. Reducing hip fracture risk with risedronate in elderly women with established osteoporosis. *Clinical Interventions in Aging* 2009;**4**:445-9.

**Maugeri 2005** *{published data only}*

Maugeri D, Mamazza C, Lo Giudice F, Puglisi N, Muscoso EG, Rizzotto M, et al. Interleukin-18 (IL-18) and matrix metalloproteinase-9 (MMP-9) in post-menopausal osteoporosis. *Archives of Gerontology and Geriatrics* 2005;**40**(3):299-305.

**McClung 1996** *{published data only}*

McClung M, Bensen W. Risedronate treatment of postmenopausal women with low bone mass: preliminary data. *Osteoporosis International* 1996;**6**(Suppl 1):257.

**McClung 1998** *{published data only}*

McClung M, Bensen W G, Bolognese M, Bonnick S, Ettinger M, Harris ST. Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass. *Osteoporosis International* 1998;**8**(Suppl 3):111.

**McClung 2010a** *{published data only}*

McClung M, Bolognese M, Miller P, Sarley J, McCullough L, Brown J, et al. Bmd response to a novel delayed-release risedronate 35 mg once-a-week formulation taken with or without breakfast: One year results. *Journal of Bone and Mineral Research* 2010;**25**(S1):S124.

**McClung 2010b** *{published data only}*

McClung MR, Bolognese MA, Miller PD, Brown JP, Recker RR. BMD response to delayed-release risedronate 35 mg once-a-week formulation taken with or without breakfast (Poster Number 067). *Journal of Clinical Densitometry* 2010;**13**:132.

**McClung 2010c** *{published data only}*

McClung MR, Zanchetta JR, Benhamou CL, Balske A, Sarley J, Recker RR. Effect of a delayed-release risedronate 35 mg once-a-week formulation taken with or without breakfast on BMD. In: Osteoporosis International. Vol. 21. 2010:S25.

**McClung 2011** *{published data only}*

McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, et al. Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet. *Osteoporosis International* 2011;**21**(Suppl 1):1-10.

**Mellstrom 2004** *{published data only}*

Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines A A, et al. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcified Tissue International* 2004;**75**:462-8.

**Miller 1999** *{published data only}*

Miller E, Roux C, McClung M, Adami S, Eastell R, Ethgen D. Risedronate reduces hip fractures in patients with low femoral neck bone mineral density [abstract]. *Arthritis and Rheumatism* 1999;**42**:S287.

**Miller 1999a** *{published data only}*

Miller PD, Brown J P, Siris ES, Hoseyni M S, Axelrod DW, Bekker P J. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Paget's Risedronate/Etidronate Study Group. *American Journal of Medicine* 1999;**106**(5):513–20.

**Minisola 2019** *{published data only}*

Minisola S, Marin F, Kendler DL, Geusens P, Zerbini C A F, Russo LA, et al. Serum 25-hydroxy-vitamin D and the risk of fractures in the teriparatide versus risedronate VERO clinical trial. *Archives of Osteoporosis* 2019;**14**(1):10.

**Ohtori 2012** *{published data only}*

Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. Teriparatide accelerates lumbar posterolateral fusion in women with postmenopausal osteoporosis: prospective study. *Spine* 2012;**37**:E1464-8.

**Oktem 2008** *{published data only}*

Oktem M, Atar I, Zeyneloglu HB, Yildirir A, Kuscu E, Muderrisoglu H. Raloxifene has favourable effects on metabolic parameters but has no effect on left ventricular function in postmenopausal women. *Pharmacological Research* 2008;**57**:364-8.

**Oliveira 2015** *{published data only}*

Oliveira LG, Eis SR, Neto H M, e Moraes FB, Pires L A, Vasconcelos JW. Use of risedronate for consolidation and callus formation in Colles fractures in postmenopausal women: SOLID study. *Revista Brasileira de Ortopedia* 2015;**50**:274-82.

**Oral 2015** *{published data only}*

Oral A, Lorenc R. Compliance, persistence, and preference outcomes of postmenopausal osteoporotic women receiving a flexible or fixed regimen of daily risedronate: a multicenter, prospective, parallel group study. *Acta Orthopaedica et Traumatologica Turcica* 2015;**49**:67-74.

**Paggiosi 2014b** *{published data only}*

Paggiosi MA, Walsh JS, Peel NF, McCloskey EV, Eastell R. A comparison of the effects of three oral bisphosphonates on the peripheral skeleton in postmenopausal osteoporosis: The trio study. *Osteoporosis International* 2014;**25**(6 Supplement):S692.

**Palomba 2005** *{published data only}*

Palomba S, Orio F, Manguso F, Falbo A, Russo T, Tolino A, et al. Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. *Osteoporosis International* 2005;**16**:1141-9.

**Pawlowski 2015** *{published data only}*

Pawlowski JW, Martin BR, McCabe GP, McCabe L, Jackson GS, Peacock M, et al. Impact of equol-producing capacity and soy-isoflavone profiles of supplements on bone calcium retention in postmenopausal women: a randomized crossover trial. *American Journal of Clinical Nutrition* 2015;**102**:695-703.

**Peris 2013** *{published data only}*

Peris P, Atkinson EJ, Gossl M, Kane TL, McCready L K, Lerman A, et al. Effects of bisphosphonate treatment on circulating osteogenic endothelial progenitor cells in postmenopausal women. *Mayo Clinic Proceedings* 2013;**88**:46-55.

**Racewicz 2007** *{published data only}*

Racewicz AJ, Schofield PJ, Cahall DL, Cline GA, Burgio DE. Monthly dosing with risedronate 50 mg on three consecutive days a month compared with daily dosing with risedronate 5 mg: a 6-month pilot study. *Current Medical Research and Opinion* 2007;**23**:3079-89.

**Ralston 2011** *{published data only}*

Ralston SH, Binkley N, Boonen S, Kiel DP, Reginster JY, Roux C, et al. Randomized trial of alendronate plus vitamin D3 versus standard care in osteoporotic postmenopausal women with vitamin D insufficiency. *Calcified Tissue International* 2011;**88**:485-94.

**Recker 2011** *{published data only}*

Recker R, Valter I, Maasalu K, Magaril C, Man Z, Zanchetta JR, et al. Bone safety of a novel delayed-release risedronate 35 mg once-a-week assessed by bone histology and histomorphometry. *Journal of Bone and Mineral Research* 2011;**26**(S1):S361-2.

**Recker 2015** *{published data only}*

Recker RR, Ste-Marie LG, Chavassieux P, McClung MR, Lundy MW. Bone safety with risedronate: histomorphometric studies at different dose levels and exposure. *Osteoporosis International* 2015;**26**:327-37.

**Reginster 2001** *{published data only}*

Reginster JY. Risedronate increases bone mineral density and reduces the vertebral fracture incidence in postmenopausal women. *Clinical and Experimental Rheumatology* 2001;**19**(2):121-2.

**Reszka 1999** *{published data only}*

Reszka AA, Halasy-Nagy JM, Masarachia PJ, Rodan GA. Bisphosphonates act directly on the osteoclast to induce caspase cleavage of mst1 kinase during apoptosis. A link between inhibition of the mevalonate pathway and regulation of an apoptosis-promoting kinase. *Journal of Biological Chemistry* 1999;**274**(49):34967-73.

**Ribot 1999** *{published data only}*

Ribot C, Smith R, Fogelman I, Pack S, Ethgen D. Risedronate increases bone mineral density and is well tolerated in postmenopausal women with low bone mineral density. *Journal of Bone and Mineral Research* 1999;**14**:S163.

**Roux 2004** *{published data only}*

Roux C, Seeman E, Eastell R, Adachi J, Jackson RD, Felsenberg D, et al. Efficacy of risedronate on clinical vertebral fractures within six months. *Current Medical Research and Opinion* 2004;**20**:433-9.

**Roux 2013** *{published data only}*

Roux C, Fahrleitner-Pammer A, Ho PR, Hawkins F, Hofbauer LC, Micaelo M, et al. Denosumab versus risedronate: efficacy and safety in postmenopausal women suboptimally adherent to alendronate therapy in a randomized open-label study. *Annals of Rheumatic Diseases* 2013;**72**:A306.

**Sebba 2004** *{published data only}*

Sebba AI, Bonnick SL, Kagan R, Thompson DE, Skalky C S, Chen E, et al. Response to therapy with once-weekly alendronate 70 mg compared to once-weekly risedronate 35 mg in the treatment of postmenopausal osteoporosis. *Current Medical Research and Opinion* 2004;**20**:2031-41.

**Seeman 2010a** *{published data only}*

Seeman E, Chapurlat R, Cheung A, Felsenberg D, La-Roche M, Reeve J, et al. Risedronate reduces micro-structural deterioration of cortical bone accompanying menopause. *Osteoporosis International* 2010;**21**(Suppl 1):S9.

**Seibel 2004** *{published data only}*

Seibel MJ, Naganathan V, Barton I, Grauer A. Relationship between pretreatment bone resorption and vertebral fracture incidence in postmenopausal osteoporotic women treated with risedronate. *Journal of Bone and Mineral Research* 2004;**19**:323-9.

**Shiraki 2003** *{published data only}*

Shiraki M, Fukunaga M, Kushida K, Kishimoto H, Taketani Y, Minaguchi H, et al. A double-blind dose-ranging study of risedronate in Japanese patients with osteoporosis (a study by the Risedronate Late Phase II Research Group). *Osteoporosis International* 2003;**14**:225-34.

**Singer 1995** *{published data only}*

Singer FR, Minoofar PN. Bisphosphonates in the treatment of disorders of mineral metabolism. *Therapeutic Advances in Endocrinology and Metabolism* 1995;**6**:259-88.

**Ste-Marie 2009** *{published data only}*

Ste-Marie LG, Brown J P, Beary JF, Matzkin E, Darbie LM, Burgio DE, et al. Comparison of the effects of once-monthly versus once-daily risedronate in postmenopausal osteoporosis: a phase II, 6-month, multicenter, randomized, double-blind, active-controlled, dose-ranging study. *Clinical Therapeutics* 2009;**31**:272-85.

**Stovall 2010** *{published data only}*

Stovall DW, Beard MK, Barbier S, Chen E, Rosenberg E, e Papp AE. Response to oral bisphosphonates in subgroups of younger and older postmenopausal women. *Journal of Women's Health* 2010;**19**:491-7.

**Sunyecz 2009** *{published data only}*

Sunyecz JA. Once-a-month risedronate in postmenopausal osteoporosis. *Postgraduate Medicine* 2009;**121**:42-4.

**Takada 2007** *{published data only}*

Takada J, Iba K, Imoto K, Yamashita T. Changes in bone resorption markers among Japanese patients with postmenopausal osteoporosis treated with alendronate and risedronate. *Journal of Bone and Mineral Metabolism* 2007;**25**:142-6.

**Tanaka 2014** *{published data only}*

Tanaka S, Miyazaki T, Uemura Y, Kuroda T, Miyakawa N, Nakamura T, et al. Design of a randomized clinical trial of concurrent treatment with vitamin K2 and risedronate compared to risedronate alone in osteoporotic patients: Japanese Osteoporosis Intervention Trial-03 (JOINT-03). *Journal of Bone and Mineral Metabolism* 2014;**32**:298-304.

**Taquet 1996** *{published data only}*

Taquet AN, Clemmensen B. A three-year double-blind placebo-controlled study of risedronate in postmenopausal osteoporosis. *Osteoporosis International* 1996;**6**(Suppl 1):262.

**Thomson 2002** *{published data only}*

Thomson AB, Marshall JK, Hunt RH, Provenza JM, Lanza FL, Royer MG, et al. 14 Day endoscopy study comparing risedronate and alendronate in postmenopausal women stratified by Helicobacter pylori status. *Journal of Rheumatology* 2002;**29**:1965-74.

**Watts 1998** *{published data only}*

Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinology and Metabolism Clinics of North America* 1998;**27**(2):419-39.

**Watts 1999** *{published data only}*

Watts N, Roux C, Genant H, Adami S, Hangartner T, Miller P. Risedronate reduces vertebral fracture risk after the first year of treatment in postmenopausal women with established osteoporosis. *Journal of Bone and Mineral Research* 1999;**14**(Suppl 1):S136.

**Watts 2003** *{published data only}*

Watts NB, Josse RG, Hamdy RC, Hughes RA, Manhart MD, Barton I, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. *Journal of Clinical Endocrinology and Metabolism* 2003;**88**:542-9.

**Watts 2008** *{published data only}*

Watts NB, Chines A, Olszynski WP, McKeever CD, McClung M R, Zhou X, et al. Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporosis International* 2008;**19**:365-72.

**Zegels 2001** *{published data only}*

Zegels B, Eastell R, Russell RG, Ethgen D, Roumagnac I, Collette J, et al. Effect of high doses of oral risedronate (20 mg/day) on serum parathyroid hormone levels and urinary collagen cross-link excretion in postmenopausal women with spinal osteoporosis. *Bone* 2001;**28**:108-12.

**Zerbini 2017** *{published data only}*

Zerbini CA Geusens P, Lespessailles E, Body JJ, Casado E, Stepan J, et al. Teriparatide compared with risedronate and the risk of clinical vertebral fractures: 2-year results of a randomized, double-dummy clinical trial. *Arthritis and Rheumatology* 2017;**69**(Suppl 10):Abstract Number: 320.

**Zoehrer 2006** *{published data only}*

Zoehrer R, Roschger P, Paschalis, EP, Hofstaetter JG, Durchschlag E, Fratzl P, et al. Effects of 3- and 5-year treatment with risedronate on bone mineralization density distribution in triple biopsies of the iliac crest in postmenopausal women. *Journal of Bone and Mineral Research* 2006;**21**(7):1106-12.

## References to studies awaiting assessment

**Benhamou 2013** *{published data only}*

Benhamou CL, Seefried L, Agodoa I, Vanden Bergh JP, Prince RL, Josse RG, et al. Treatment satisfaction in postmenopausal women suboptimally adherent to alendronate who transitioned to denosumab vs risedronate. Osteoporosis International 2013;**24**(1 Suppl 1):S159-60.

**Bilek 2016** *{published data only}*

Bilek LD, Waltman NL, Lappe JM, Kupzyk KA, Mack LR, Cullen DM, et al. Protocol for a randomized controlled trial to compare bone-loading exercises with risedronate for preventing bone loss in osteopenic postmenopausal women. BMC Womens Health 2016;**16**(1):59.

**Deng 2020** *{published data only}*

Deng Y, Li L, Li C, Wang F, Qu Y. Efficacy of combined medication of risedronate sodium and selective estrogen receptor modulator on the postmenopausal osteoporosis. *Pakistan Journal of Pharmaceutical Sciences* 2000;**33**(1 (Special)):495-8.

**Felsenberg 2010** *{published data only}*

Felsenberg D, Charpulat R, Cheung AM, LaRoche M, Morris E, Seeman E, et al. Longitudinal in vivo micro-CT assessment in osteopenic women demonstrated that risedronate reduced the deterioration of cortical bone. Bone 2010;**47**(Supplement 1):S35.

**Hagino 2014** *{published data only}*

Hagino H, Kishimoto H, Ohishi H, Horii S, Nakamura T. Efficacy, tolerability and safety of once-monthly administration of 75 mg risedronate in Japanese patients with involutional osteoporosis: A comparison with a 2.5 mg once-daily dosage regimen. *Bone* 2014;**59**:44-52.

**Ia Vilariño 2009** *{published data only}*

Ia Vilariño S, Vilarino C, Schwartz A, Contreras Ortiz O, Dotto J. Comparison of different treatments on postmenopausal patients (POSTM). In: Maturitas. Vol. 63. 2009:S95.

**Lim 2019** *{published data only}*

Lim HH, Lim SJ, Park YS, Choi SH, Min YK, Yoon BK. Effects of risedronate versus menopausal hormone therapy on bone mineral density in postmenopausal Korean women with

hip fracture: a randomized, open-label trial. *Maturitas* June 2019;**124**:143.

**Matsuzaki 2012** *{published data only}*

Matsuzaki K, Ito, Kaneko H, Kato M, Hikata T, Nango N, et al. Efficacy of osteoporotic agents in trabecular microstructure (SU0313). Journal of Bone and Mineral Research 2012;**27**(S1):S304.

**NCT00345644** *{published data only}*

NCT00345644. Risedronate in osteopenic postmenopausal women (OSMAUSE) [A non-invasive evaluation of bone microarchitecture modification in osteopenic postmenopausal women by 3D peripheral quantitative computed tomography: a 24 month, monocenter study comparing weekly oral risedronate 35 mg and placebo]. clinicaltrials.gov/ct2/show/NCT00345644 (first received 28 June 2006).

**NCT00386360** *{published data only}*

NCT00386360. Study of the effect of once a week risedronate on the microstructure of tibia and radius using a new scanning method [A non-invasive evaluation of bone microarchitecture modification in osteopenic postmenopausal women by 3D-Peripheral Quantitative Computed Tomography (3D-pQCT)]. clinicaltrials.gov/ct2/show/NCT00386360 (first received 11 January 2012).

**NCT00402441** *{published data only}*

NCT00402441. Risedronate in thepPrevention of osteoporosis in postmenopausal women [A one-year, multicenter, randomized, double-blind, placebo-controlled, parallel group study to determine the efficacy and safety of 35-mg risedronate administered once a week in the prevention of osteoporosis in postmenopausal women]. clinicaltrials.gov/ct2/show/NCT00402441 (first received 22 November 2006).

**NCT00790101** *{published data only}*

NCT00790101. Risedronate vs raloxifene in hormone replacement therapy discontinuation [An 18-month, multicenter, parallel-group study to determine the relative efficacy of risedronate versus raloxifene in subjects who have discontinued hormone replacement therapy (HRT) for early intervention in osteoporosis]. clinicaltrials.gov/ct2/show/NCT00790101 (first received 13 November 2008).

**NCT01904110** *{published data only}*

NCT01904110. To evaluate the efficacy and the safety of monthly versus weekly oral risedronate with vitamin D in compliance, improvement of vitamin D and BMD in Korean postmenopausal osteoporotic women [ For 12 months, the multi center, randomized, open-label comparative clinical study to evaluate the efficacy and the safety of monthly (RisenexM Group) versus weekly oral risedronate (Risenexsplus Group) with vitamin D in compliance, improvement of vitamin D and BMD in Korean postmenopausal osteoporotic women (Phase IV)]. clinicaltrials.gov/ct2/show/NCT01904110 (first received 22 July 2013).

**Okamoto 2010** *{published data only}*

Okamoto K, Inaba M, Furumitsu Y, Ban A, Mori N, Yukioka K, et al. Beneficial effect of risedronate on arterial thickening and stiffening with a reciprocal relationship to its effect on bone mass in female osteoporosis patients: a longitudinal study. *Life Sciences* 2010;**87**:686-91.

**Pastore 2014** *{published data only}*

Pastore R, Bultrini A, DiGiacinto P, Cannuccia A, Frontoni S. Sequentialtherapy in severe osteoporosis. In: Osteoporosis International. Vol. 25. 2014:S254.

**Seeman 2010** *{published data only}*

Seeman E, Borah B, Chapurlat R, Felsenberg D, Darbie L, Rizzoli R. Risedronate reduces deterioration of cortical bone microarchitecture accompanying menopause. In: Journal of Bone and Mineral Research. Vol. 26. 2010:S32.

**UMIN000010017** *{published data only}*

UMIN000010017. Efficacy of bazedoxifene on vascular endothelial function in postmenopausal women with osteoporosis. ictrptest.azurewebsites.net/Trial2.aspx?TrialID=JPRN-UMIN000010017 (first received 19 Feburay 2013).

**Yeter 2014** *{published data only}*

Yeter A, Kavuncu V, Evcik FD, Demirdal US, Subasi V, Cakir T. Evalution the effects of raloxifene and risedronate on serum biochemical markers. *Turkish Journal of Osteoporosis* 2014;**20**:110-6.

**Yildirim 2005** *{published data only}*

Yildirim K, Gureser G, Karatay S, Melikoglu MA, Ugur M, Erdal A, et al. Comparison of the effects of alendronate, risedronate and calcitonin treatment in postmenopausal osteoporosis. *Journal of Back and Musculoskeletal Rehabilitation* 2005;**18**:85-9.

## Additional references

**AACE guidelines 2020**

Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update. *Endocrine Practice* 2020;**26**(Suppl 1):1-46.

**Barrionuevo 2019**

Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2019;**104**(5):1623-30.

**Black 2001**

Black DM, Steinbuch M, Palermo L, Dargent-Molina P, Lindsay R, Hoseyni MS, et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos International* 2001;**12**(7):519-28.

**Body 2020**

Body JJ, Marin F, Kendler DL, Zerbini CA, López-Romero P, Möricke R. Efficacy of teriparatide compared with risedronate on FRAX® -defined major osteoporotic fractures: results of the VERO clinical trial.. *Osteoporosis International* 2020;**31**:935-42.

**Brown 2002b**

Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Canadian Medical Association Journal* 2002;**167**(10 Suppl):S1-34.

**Cauley 2000**

Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporosis International* 2000;**11**(7):556-61.

**Chandran 2019**

Chandran T, Venkatachalam I. Efficacy and safety of denosumab compared to bisphosphonates in improving bone strength in postmenopausal osteoporosis: a systematic review. *Singapore Medical Journal* 2019;**60**(7):364-78.

**Crandall 2014**

Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Booth MJ, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. *Annals of Internal Medicine* 2014;**161**(10):711-23.

**Cranney 2002**

Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocrine Reviews* 2002;**23**(4):517-23.

**Cummings 1989**

Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. *Archives of Internal Medicine* 1989;**149**(11):2445-8.

**Deeks 2019**

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). In: Cochrane Handbook for Systematic Reviews of Interventions version 6.0. The Cochrane Collaboration, July 2019:Available from www.training.cochrane.org/handbook.

**Dixon 2003**

Dixon P. The p-value fallacy and how to avoid it. *Canadian Journal of Experimental Psychology* 2003;**57**(3):189-202.

**Doherty 2001**

Doherty DA, Sanders KM, Kotowicz MA, Prince RL. Lifetime and five-year age-specific risks of first and subsequent osteoporotic fractures in postmenopausal women. *Osteoporosis International* 2001;**12**(1):16-23.

**Eastell 2019**

Eastell R, Rosen C J, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological Management of osteoporosis in postmenopausal women: an Endocrine Society* Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2019;**104**(5):1595-622.

**Edwards 2013**

Edwards BJ, Bunta AD, Lane J, Odvina C, Rao DS, Raisch DW, et al. Bisphosphonates and nonhealing femoral fractures: analysis of the FDA Adverse Event Reporting System (FAERS) and international safety efforts: a systematic review from the Research on Adverse Drug Events And Reports (RADAR) project. *Journal of Bone and Jjoint Surgery* 2013;**95**(4):297-307.

**Ellis 2014**

Ellis AG, Reginster JY, Luo X, Cappelleri JC, Chines A, Sutradhar S, et al. Bazedoxifene versus oral bisphosphonates for the prevention of nonvertebral fractures in postmenopausal women with osteoporosis at higher risk of fracture: a network meta-analysis. *Value in Health* 2014;**17**(4):424-32.

**EPOC 2018**

Cochrane Effective and Organisation of Care (EPOC). Reporting the effects of an intervention in EPOC review. EPOC Resources for review authors 2018;**https://epoc.cochrane.org/resources/epoc-resources-review-authors (accessed 27 October 2020)**.

**FDA Drug Approval Package-Actonel® 2000**

FDA Drug Approval Package-Actonel®. Risedronate Sodium Tablets Application No.: 20-835/S1, S2, S3 & S4 2000:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20835S001_Actonel.cfm.

**Fink 2005**

Fink HA, Milavetz DL, Palermo L, Nevitt MC, Cauley JA, Genant HK, et al. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? *Journal of Bone and Mineral Research* 2005;**20**(7):1216-22.

**GRADE 2015**

GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University . 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

**Greenspan 2001**

Greenspan SL, von Stetten E, Emond K, Jones L, Parker RA. Instant vertebral assessment: a noninvasive dual X-ray absorptiometry technique to avoid misclassification and clinical mismanagement of osteoporosis. *Journal of Clinical Densitometry* 2001;**4**(4):373-80.

**Health Canada Product Monograph-Actonel® 2017**

Health Canada Product Monograph-Actonel®. Risedronate Sodium tablets 5 mg, 30 mg, 35 mg, 150 mg, and delayed release 35 mg 2017:https://pdf.hres.ca/dpd_pm/00040591.PDF.

**Hewitt 2005**

Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral bloodgdT cells in response to aminobisphosphonates is inhibited by statins. *Clinical and Experimental Immunology* 2005;**139**:101-11.

**Higgins 2017**

Higgins JP, Altman DG, Sterne JA (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP,

Churchill R, Chandler J, Cumpston MS (editors). In: Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017:Available from www.training.cochrane.org/handbook.

**Higgins 2020**

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

**Higgins 2021**

Higgins JP, Lasserson T, Chandler J, Tovey D, Thomas J, Flemyng E, et al. Methodological Expectations of Cochrane Intervention Reviews. Cochrane: London, version February 2021.

**Hodsman 2002**

Hodsman AB, Hanley DA, Josse R. Do bisphosphonates reduce the risk of osteoporotic fractures? An evaluation of the evidence to date. *Canadian Medical Association Journal* 2002;**166**(11):1426-30.

**Hopkins 2011**

Hopkins RB, Goeree R, Pullenayegum E, Adachi JD, Papaioannou A, Xie F, et al. The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. *BMC Musculoskeletal Disorders* 2011;**12**:209. doi: 10.1186/1471-2474-12-209.

**Jansen 2011**

Jansen JP, Bergman GJ, Huels J, Olson M. The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-non hip fractures in osteoporosis: a network meta-analysis. *Seminars in Arthritis and Rheumatism* 2011;**40**(4):275-84. doi: 10.1016/j.semarthrit.2010.06.001.

**Johnell 2006**

Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis International* 2006;**17**:1726-33.

**Kanis 2013**

Kanis JA, Borgström F, Compston J, Dreinhöfer K, Nolte E, Jonsson L, et al. SCOPE: a scorecard for osteoporosis in Europe. *Archives of Osteoporosis* 2013;**8**(1-2):144.

**Khow 2017**

Khow KS, Shibu P, Yu SC, Chehade MJ, Visvanathan R. Epidemiology and postoperative outcomes of atypical femoral fractures in older adults: a systematic review. *Journal of Nutrition, Health and Aging* 2017;**21**(1):83-91.

**Langsetmo 2009**

Langsetmo L, Goltzman D, Kovacs CS, Adachi JD, Hanley DA, Kreiger N, et al. Repeat low-trauma fractures occur frequently among men and women who have osteopenic BMD. *Journal of Bone and Mineral Research* 2009;**24**(9):1515-22.

**Lee 2014**

Lee SH, Chang SS, Lee M, Chan RC, Lee CC. Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. *Osteoporosis International* 2014;**25**(3):1131-9.

**Liu 2018**

Liu GF, Wang ZQ, Liu L, Zhang BT, Miao YY, Yu SN. A network meta-analysis on the short-term efficacy and adverse events of different anti-osteoporosis for the treatment of postmenopausal osteoporosis. *Journal of Cell Biochemistry* 2018;**119**(6):4469-81.

**Mavrokokki 2007**

Mavrokokki T, Cheng A, Stein B, Gross A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *Journal of Oral Maxillofacial Surgery* 2007;**65**:415-23.

**McGowan 2016**

McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *Journal of Clinical Epidemiology* 2016;**75**:40-6.

**Meier 2012**

Meier RP, Perneger TV, Stern R, Rizzoli R, Peter RE. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. *Archives of Internal Medicine* 2012;**172**(12):930-6.

**Melton 2013**

Melton LJ, Achenbach SJ, Atkinson EJ, Therneau TM, Amin S. Long-term mortality following fractures at different skeletal sites: a population-based cohort study. *Osteoporosis International* 2013;**24**(5):1689-96.

**Migliore 2013**

Migliore A, Broccoli S, Massafra U, Cassol M, Frediani B. Ranking antireabsorptive agents to prevent vertebral fractures in postmenopausal osteoporosis by mixed treatment comparison meta-analysis. *European Review for Medical and Pharmacological Sciences* 2013;**17**(5):658-67.

**Newell 1992**

Newell DJ. Intention-to- treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

**NIH Consensus 2001**

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;**285**(6):785-95.

**NOGG 2017**

NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis. National Osteoporosis Guideline Group Updated March 2017.

**Olson 2007**

Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. *Journal of Oncology Pharmacy Practice* 2007;**13**(4):223-9.

**Pasco 2006**

Pasco J A, Seeman E, Henry M J, Merriman E N, Nicholson G C, Kotowicz M A. The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporosis International* 2006;**17**(9):1404-9.

**Rohatgi 2018 [Computer program]**

WebPlotDigitizer Version: 4.2. Rohatgi A. San Francisco, California, USA, April, 2019.

**Schünemann 2013**

Schünemann H, Brożek J, Guyatt G, Oxman A (editors). GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, Updated October 2013. Available from guidelinedevelopment.org/handbook.

**Sharma 2014**

Sharma A, Einstein, AJ, Vallakati A, Arbab-Zadeh A, Walker MD, Mukherjee D. Risk of atrial fibrillation with use of oral and intravenous bisphosphonates. *American Journal of Cardiology* 2014;**113**(11):1815-21.

**Tadrous 2014**

Tadrous M, Wong L, Mamdani MM, Juurlink DN, Krahn MD, Levesque LE, et al. Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis. *Osteoporosis International* 2014;**25**(4):1225-35.

**Taggart 2002**

Taggart H, Bolognese MA, Lindsay R, Ettinger MP, Mulder H, Josse RG, et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clinic Proceedings* 2002;**77**(3):262-70.

**Tran 2017**

Tran T, Bliuc D, van Geel T, Adachi JD, Berger C, van den Bergh J, et al. Population-Wide Impact of non-hip non-vertebral fractures on mortality. *Journal of Bone and Mineral Research* 2017;**32**(9):1802-10.

**van der Velde 2017**

van der Velde RY, Wyers CE, Teesselink E, Geusens PP, van den Bergh JP, de Vries F, et al. Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: variation by age, sex, geographic location and ethnicity. *Bone* 2017;**94**:50-5.

**Wade 2014**

Wade SW, Strader C, Fitzpatrick LA, Anthony MS, O'Malley CD. Estimating prevalence of osteoporosis: examples from industrialized countries. *Archives of Osteoporosis* 2014;**9**:182.

**Wainwright 2005**

Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, et al. Hip fracture in women without osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(5):2787-93.

**WHO 1994**

World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO study group. World Health Organ Technical Report Series: 843 1994.

**WHO 2004**

WHO scientific group on the assessment of osteoporosis at primary health care level: summary meeting report. World Health Organization (WHO) 2003. Available at: http://www.who.int/chp/topics/Osteoporosis.pdf. Accessed February 6, 2020.

**Wysowski 2013**

Wysowski DK, Greene P. Trends in osteoporosis treatment with oral and intravenous bisphosphonates in the United States, 2002-2012. *Bone* 2013;**57**(2):423-8.

**Yang 2016**

Yang XC, Deng ZH, Wen T, Luo W, Xiao WF, Zhao RB, et al. Network meta-analysis of pharmacological agents for osteoporosis treatment and fracture prevention. *Cellular Physiology and Biochemistry* 2016;**40**(3-4):781-95.

**Zhou 2016**

Zhou J, Ma X, Wang T, Zhai S. Comparative efficacy of bisphosphonates in short-term fracture prevention for primary osteoporosis: a systematic review with network meta-analyses. *Osteoporosis International* 2016;**27**(11):3289-300.

## References to other published versions of this review

**CADTH 2006b**

Wells GA, Cranney A, Bouchere M, Peterson J, Shea B, Robinson V, et al. Bisphosphonates for the primary and secondary prevention of osteoporotic fractures in postmenopausal women: a meta-analysis [Technology report no 69]. Ottawa: Canadian Agency for Drugs and Technologies in Health 2006.

**Cranney 2003**

Cranney A, Waldegger L, Zytaruk N, Shea B, Weaver B, Papaioannou A, et al. Risedronate for the prevention and treatment of postmenopausal osteoporosis. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No: CD004523. [DOI: 10.1002/14651858.CD004523]

**Cranney 2006**

Cranney A, Adachi JD, Guyatt G, Papaioannou A, Robinson V, Shea B, et al. Risedronate for the prevention and treatment of postmenopausal osteoporosis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No: CD004523. [DOI: 10.1002/14651858.CD004523.pub2]

**Wells 2008**

Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane*

*Database of Systematic Reviews* 2008, Issue 1. Art. No: CD004523. [DOI: 10.1002/14651858.CD004523.pub3]

* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Akyol 2006

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Blinding: NR<br>Trial completion: NR/112<br>Risedronate: NR/52<br>Alendronate: NR/60 |
| Participants | Inclusion criteria: at least one year duration of menopause;the diagnosis of osteoporosis was based on clinical evaluation, lateral spinal graphs, lumbar vertebra and femur bone mineral density, DEXA (Dual Energy X-ray Absorptiometry) (Norland Excell, USA) with lumbar vertebrae (L2-L4) anterior-posterior and left femur (total femur) before treatment and was performed twice, after one year of treatment; WHO (T-score -2.5 and below) on the basis of the criteria patients were included in our study.<br>Exclusion criteria: bone and calcium metabolism diseases or medications that may affect the patients who first used drugs to treat osteoporosis were studied were excluded from the study.<br>Age: 56.7 (8.0) years<br>Time since menopause: 12.9 (8.9) years<br>Mean BMI: 26.1 (2.7) kg/m$^2$<br>Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: -2.94 (0.81), femoral neck T-score: -1.44 (0.89)<br>Prevalent vertebral fractures: NR<br>Baseline serum vitamin D: NR<br>Previous bisphosphonate experience: NR<br>Source: Turkey<br>Race: NR |
| Interventions | Two-arm comparison:<br>1. Risedronate 35 mg once weekly<br>2. Alendronate 70 mg once weekly<br>(All participants received daily calcium 1000 mg.) |
| Outcomes | Zero clinical vertebral, non-vertebral, hip, wrist and atypical femoral fractures were all inferred from "we did not observe the fracture", and assessed as safety outcomes. The ascertainment was not provided. |

**Akyol 2006** *(Continued)*

| | |
|---|---|
| | None of the safety outcomes of Interest were reported. |
| Notes | 1. Funding information: NR<br>2. The publication is in Turkish and was translated by online Google Translate Service. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were randomly classified into two groups. Group I (n=60) received alendronate Na (70 mg/week) and group II (n=52) received risedronate Na (35 mg/week)"<br>Method of sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | High risk | Blinding was not mentioned and probably open-label designed given two medications were different in appearance. The participants 'and personnel's performance were likely subject to high risk of bias. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding appeared infeasible. However, the assessment for objective outcomes was mainly based on clinical evidence and criteria, which was less likely to be biased. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | None of the subjective outcomes were reported. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | This publication was translated. Total withdrawals or reasons for discontinuation were not provided in the study, and the efficacy population was not described. Fracture was extracted as an adverse event in the Discussion "We did not observe the fracture." It was judged to be at unclear risk of bias. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | None of the safety outcome data of interest was extracted. |
| Selective reporting (reporting bias) | Unclear risk | Protocol was not found and fractures (or lack thereof) was reported in the discussion. Primary outcome was unclear. This publication was translated by online software "google translate" and the information was probably limited. |
| Other bias | Unclear risk | This publication was translated and the information was very limited. |

**Anastasilakis 2008a**

***Study characteristics***

| | |
|---|---|
| Methods | Randomised and active-controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Blinding: open-label |

**Anastasilakis 2008a** *(Continued)*

| | |
|---|---|
| | Trial completion: 44/44 (100%)<br><br>Risedronate: 22/22 (100%)<br><br>Teriparatide: 22/22 (100%) |
| Participants | Inclusion criteria: postmenopausal Caucasian women (age 65.1 ± 1.6 years, age at menopause 47.3 ± 1.1 years) with osteoporosis (T-score < -2.5).<br><br>Exclusion criteria: anti-osteoporotic treatment during the last year and diseases and/or medications that could affect bone turnover.<br><br>Age: 65.1 (1.6) years<br><br>Time since menopause: 17.8 (1.0) years<br><br>Mean BMI: 28.2 (1.7) kg/$m^2$<br><br>Lumbar spine BMD: 0.76 (0.01) g/$cm^2$, femoral neck BMD: NR<br><br>Lumbar spine T-score: NR, femoral neck T-score: NR<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: Greece<br><br>Race: Caucasian (100%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 35 once weekly<br><br>2 Teriparatide 20 µg/day, SC<br><br>(All participants received daily calcium 500 mg and vitamin D 400 IU.) |
| Outcomes | None of the fracture outcome of interest was reported.<br><br>Safety was monitored with the recording of clinical and laboratory adverse events at each study visit. Three safety outcomes, including withdrawals due to adverse events, serious adverse events, and gastrointestinal adverse events were reported. |
| Notes | Funding information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomised, open-label trial"<br>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 | It was an open-label trial involving different dose regimens and routes of administration. The differences between two treatments would likely influence the participants' and personnel' performance. |
| Blinding of outcome assessment (detection bias) | Unclear risk | None of objective outcomes of interest, fracture outcomes, were reported. |

**Anastasilakis 2008a** *(Continued)*

| | | |
|---|---|---|
| Objective outcomes | | |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | It was an open-label trial, where the participants', investigators', and assessors' knowledge about the allocated interventions would bias the assessment of subjective outcomes. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Quote: ""All women were able to complete the study protocol". It was judged to be at low risk of bias given that no missing data would bias the estimate of safety outcomes of interest. |
| 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 appeared to be free of other risks of bias. |

**Atmaca 2006**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Blinding: NR<br>Trial completion: NR/30<br>Risedronate: NR/14<br>Alendronate: NR/16 |
| Participants | Inclusion criteria: postmenopausal women with a mean age of 66.3 years (range, 60 to 85 years), and a duration of menopause of at least 2 years (since last menstrual period). Osteoporosis was diagnosed in accordance with World Health Organization criteria, and women with a T-score less than -2.5 were included in the study.<br>Exclusion criteria: any medication known to affect bone metabolism, such as oestrogens, progestins, calcitonin, fluoride, bisphosphonates, corticosteroids, vitamin D in pharmacologic doses, and antiepileptics for the previous 6 months, scoliosis and severe spinal osteoarthritis; any medical condition that may affect bone metabolism, such as cancer and abnormal uterine bleeding for 5 years; untreated endocrinological disease, liver and kidney failure, alcohol or drug addiction, severe psychiatric disorder, hypocalcaemia or hypercalcaemia, history of hip or vertebral fracture, and history of oesophagitis and peptic ulcer disease; and other metabolic bone disorders such as Paget's disease, hyperparathyroidism, and osteomalacia.<br>Age: 66.0 (3.8) years<br>Time since menopause: 15.5 (4.7) years<br>Mean BMI: NR<br>Lumbar spine BMD: 0.66 (0.08) g/cm$^2$, femoral neck BMD: 0.60 (0.06) g/cm$^2$<br>Lumbar spine T-score: NR, femoral neck T-score: NR |

**Atmaca 2006** *(Continued)*

| | |
|---|---|
| | Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: Turkey<br><br>Race: NR |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Alendronate 10 mg/day<br><br>(All participants received daily calcium 600 mg and vitamin D 400 IU.) |
| Outcomes | None of the fracture outcomes of interest were reported.<br><br>Two safety outcomes, withdrawals due to adverse events and serious adverse events, were inferred as zero from the text Quote: "None of the women experienced any adverse events." The ascertainment was not specified. |
| Notes | Funding information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "This prospective, randomised study... "<br>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 very likely an open-label head-to-head comparison trial where the placebo of each other drug were probably not used. Although both were bisphosphonates with same dose regimens and similar precautions, it was not clear how they looked (similarity). The participants and personnel would likely know what they were prescribed. |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | None of the objective outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | High risk | Blinding was not mentioned. However, it is very likely to be an open-label head-to-head comparison trial where the placebo of each other drug were probably not used, therefore the participants', investigators', and assessors' knowledge about the allocated interventions would likely bias the assessment of subjective outcomes. |
| Incomplete outcome data (attrition bias)<br>Efficacy outcomes | Unclear risk | None of the objective outcome data were extracted. |
| Incomplete outcome data (attrition bias)<br>Safety Outcomes | Unclear risk | Two safety outcomes, withdrawals due to adverse events and serious adverse events, were inferred and extracted. No information about the attrition was provided and it is not clear wether there was missing data biasing the estimate of effect size. |

**Atmaca 2006** *(Continued)*

| | | |
|---|---|---|
| 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 appeared to be free of other risks of bias. |

**Bala 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and placebo-controlled trial<br>Primary prevention<br>Duration: 12 months<br>Blinding: double-blind<br>Trial completion: 287/324 (89%)<br>Risedronate: 195/221 (88%)<br>Placebo: 92/103 (89%) |
| Participants | Inclusion criteria: Group 1: women younger than 55 years (mean age 53 years; range, 44–55 years) with BMI between 18 and 28 kg/m$^2$; Group 2: women older than 55 years (mean age 60 years; range, 55-76 years) with similar range in BMI. The entry criteria in both studies required a T-score at the lumbar spine (LS, L1-L4) of -1 to -2.5 SD, and at the total hip T-score ≥ -2.5 SD, or a LS T-score ≥ -2.5 SD and at the total hip T-score between -1 and -2.5 SD.<br>Exclusion criteria: previous or current use of glucocorticoids, anabolic steroids, estrogens, fluorides, bisphosphonates, or calcium or vitamin D supplementation.<br>Age: 57 (6) years<br>Time since menopause: NR<br>Mean BMI: 23 (3) kg/m$^2$<br>Lumbar spine BMD: 0.89 (0.07) g/cm$^2$, femoral neck BMD: 0.80 (0.09) g/cm$^2$<br>Lumbar spine T-score: -1.76 (0.52), femoral neck T-score: -1.23 (0.75)<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: 0/324 (0%)<br>Source: Australia, France, Canada, Germany, UK, Argentina, and Switzerland<br>Race: NR |
| Interventions | Two-arm comparison:<br>1. Risedronate 35 mg once weekly<br>2. Placebo once weekly<br>(All participants received daily calcium 500 mg and vitamin D 400 IU.) |
| Outcomes | None of the fracture outcome of interest was reported. |

**Bala 2014** *(Continued)*

| | |
|---|---|
| | One safety outcome, withdrawals due to adverse events was reported. Assessment methods were not described. |
| Notes | Funded by Warner Chilcott (US) LLC and Sanof. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Women were randomised 2:1 to either oral risedronate (35 mg/week) or an oral placebo for 12 months."<br>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 | Quote: "...two similarly designed double-blind placebo-controlled studies..."<br>Blinding approach was not provided. It was not clear how the placebo was alike risedronate and whether it was prescribed with the same regimen (weekly) and precautions. |
| Blinding of outcome assessment (detection bias)<br>Objective outcomes | Unclear risk | None of the objective outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias)<br>Subjective outcomes | Unclear risk | Quote: "...two similarly designed double-blind placebo-controlled studies..."<br>Blinding approach was not provided. It was not clear if the blinding was effective to prevent the participants, investigators, and assessors knowing the allocated interventions after assignment. |
| Incomplete outcome data (attrition bias)<br>Efficacy outcomes | Unclear risk | None of the objective outcome data were extracted. |
| Incomplete outcome data (attrition bias)<br>Safety Outcomes | Low risk | Only one safety outcome of interest, WDAE, was extracted. All randomised participants seemed to take medication and included in the analysis. The 1-year completion rates were 89% (92/103) in placebo group and 88% (195/221) in risedronate group. All randomised participants were accounted for and it was at very 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 method section. |
| Other bias | Low risk | It appeared to be free of other risks of bias. |

**Brown 2002**

***Study characteristics***

| | |
|---|---|
| Methods | Randomised and active-controlled trial<br>Secondary prevention<br>Duration: 24 months<br>Blinding: double-blind |

**Brown 2002** *(Continued)*

| | |
|---|---|
| | Trial completion: 1127/1456 (77%)<br><br>Risedronate 5 mg/day: 378/480 (79%)<br><br>Risedronate 35 mg/week: 370/485 (76%)<br><br>Risedronate 50 mg/week: 379/491 (77%) |
| Participants | Inclusion criteria: ambulatory women in generally good health if they were 50 years or older, 5 years since menopause elapsed, had at least 3 evaluable lumbar spine vertebral bodies without fracture or degenerative disease. Women required to have either (1) low lumbar spine BMD (lower than 0.772 g/cm² by Hologic instrument or 0.880 g/cm² by Lunar instrument) or low total proximal femur BMD (lower than 0.637 g/cm² by Hologic or 0.694 g/cm² by Lunar) or (2) low lumbar spine BMD (defined as value lower than 0.827 g/cm² by Hologic and 0.940 g/cm² by Lunar) and at least one prevalent vertebral fracture (T4-L4). These correspond to approximately -2.5 for participants enrolled on the basis of BMD only, and -2.0 for participants enrolled on the basis of lumbar spine BMD and prevalent vertebral fracture. Subjects less than 65 years who had hysterectomy without bilateral ovariectomy were to have FSH levels greater than 50 IU/mL and estradiol E2 levels less than 73 pmol/L to ensure they were postmenopausal. Women were not excluded specifically because of previous or active gastrointestinal (GI) illness or concomitant use of aspirin/NSAIDs.<br><br>Exclusion criteria: if had conditions that might interfere with the evaluation of spinal bone loss, or if they had received drugs known to affect bone metabolism.<br><br>Age: 67.9 (8.2) years<br><br>Time since menopause: 22.0 (10.2) years<br><br>BMI: NR<br><br>Lumbar spine BMD: NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: -3.06 (0.67), femoral neck T-score: -2.30 (0.66)<br><br>Prevalent vertebral fractures: 474 (33%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: Canada and USA<br><br>Race: NR |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Risedronate 35 mg once weekly<br><br>3. Risedronate 50 mg once weekly<br><br>(All participants received daily calcium 100 mg, and Vitamin D supplementation if Vitamin D < 30nmol/L.) |
| Outcomes | Fractures were assessed and evaluated as adverse events.<br><br>Radiographic vertebral fracture were determined at a central facility (Synarc, San Francisco, CA, USA) by a radiologist who was blinded to the treatment assignments. Lateral X-rays of the lumbar and thoracic spine taken at baseline and month 24 were compared using the semi-quantitative method.<br><br>Non-vertebral, hip and wrist fractures: non-vertebral fractures were based on adverse event reporting.<br><br>Withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events: Participant-reported adverse events were reported throughout of the study. |

**Brown 2002** *(Continued)*

| | |
|---|---|
| Notes | 1. Funded by Procter and Gamble Pharmaceuticals, Inc., Cincinnati, Ohio and Aventis Pharmaceuticals, Bridgewater, NJ, USA.<br><br>2. Two arms, risedronate 5 mg/day and 35 mg/week, have the same weekly dose so they were not included in the quantitative synthesis. The pair-wise comparisons were summarized in Table 2, Appendix 5.<br><br>The comparisons relevant to risedronate 50 mg/week (an unapproved dose) were described in Table 3, Appendix 5. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Double-blind randomised active-controlled trial; Patients stratified by centre and randomised in 1:1:1 ratio to the 3 groups"<br><br>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 | Quote: "double-blind, active-control"; " The tablets, including placebo, were identical in appearance."<br><br>Blinding methods were judged appropriate. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "...double-blind, active-control"; "New vertebral fractures were determined at a central facility (Synarc, San Francisco, CA, USA) by a radiologist who was blinded to the treatment assignments"; "Non-vertebral fractures were based on adverse event reports." "double-blind, active-control"; " The tablets, including placebo, were identical in appearance."<br><br>Outcome assessors for radiographic vertebral fractures were blinded. Other fracture outcomes were objective and would less likely to be biased even the blinding approach was not provided. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Blinding methods were judged appropriate. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Quote: "Approximately 77% of the subjects enrolled completed 24 months of treatment"; "The percentage of subjects who withdrew from the study was similar for all 3 treatment groups"completion rate around 80%; the efficacy analysis by using the ITT population.<br><br>Vertebral fractures were secondary endpoints. The completion rates were 378/480 (79%) in 5 mg group, 370/485 (76%) in 30 mg group, and 379/491 (77%) in the 50 mg group. Overall, it was 77.4% over 2 years. Reasons for withdrawal were balanced across groups, for example adverse event ranges from 12% in 50 mg weekly group to 16% in 5mg daily group. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Quote: "Withdrawals due to an adverse event were also similar for all treatment groups."<br><br>As above, the 2-year overall completion rates and reasons for early discontinuations were balanced across groups. It is judged to be at low risk of bias in this domain. |

**Brown 2002** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Protocol and NCT record were not found. However, outcomes were reported as described in the Methods section and abstract. |
| Other bias | Low risk | None was detected. |

**Clemmesen 1997**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and placebo-controlled trial<br>Secondary prevention<br>Duration: two years and one year off-drug follow-up<br>Blinding: double-blind<br>Trial completion: 93/132 (70%)<br>Risedronate 2.5 mg/day continuous: 29/44 (66%)<br>Risedronate 2.5 mg/day cyclic: 33/44 (75%)<br>Placebo: 31/44 (70%) |
| Participants | Inclusion criteria: otherwise healthy postmenopausal women, 53 to 81 years of age (mean age 68 years) and at least 1 year past the menopause, with established postmenopausal osteoporosis defined as at least one, but no more than four vertebral fractures, and at least three intact lumbar vertebrae.<br>Exclusion criteria: medications with known influence on bone metabolism, ever use of bisphosphonate or fluoride, oestrogen or calcitonin treatment within 6–12 months, secondary causes of osteoporosis.<br>Age: 68.3 (5.7) years<br>Time since menopause: 20.3 (7.3) years<br>BMI: 25.0 kg/m$^2$<br>Lumbar spine BMD: 0.78 (0.14) g/cm$^2$, femoral neck BMD: 0.61 (0.08) g/cm$^2$;<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: 132/132 (100%)<br>Previous bisphosphonate experience: 0/132 (0%)<br>Source: Denmark<br>Race: NR |
| Interventions | Three-arm comparison:<br>1. Risedronate 2.5 mg/day continuous<br>2. Risedronate 2.5 mg/day, cyclic: risedronate 2.5 mg/day for 2 weeks followed by 10 weeks of daily placebo.<br>3. Placebo<br>(All participants received daily calcium 1000 mg.) |

**Clemmesen 1997** *(Continued)*

| | |
|---|---|
| Outcomes | Radiographic vertebral and non-vertebral fractures, withdrawals due to adverse events serious adverse events, and gastrointestinal adverse events were reported. However, the data covered 1-year off-drug period so none were included in the quantitative synthesis. The reported data were listed in Table 1, Appendix 5. |
| Notes | Funding information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...a 2-year randomised, double-masked, placebo controlled, phase II trial with 1-year of follow-up"<br>The method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | The method for sequence generation was not provided. |
| Blinding of participants and personnel (performance bias) | Unclear risk | None of the outcomes of interest were extracted. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | Two objective outcomes of interest, radiographic vertebral and non-vertebral fractures, were reported. However, the reported data covered 1-year off-treatment and were not usable. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | Three subjective outcomes of interest, including withdrawal due to adverse events, serious adverse events, and gastrointestinal adverse events, were reported. However, the reported data covered 1-year off-treatment and were not usable. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | None of the safety outcome data were extracted. |
| 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 appears to be free of other risks of bias. |

**Delmas 2008a**

***Study characteristics***

| | |
|---|---|
| Methods | Randomised controlled trial<br>Secondary prevention<br>Duration: two years<br>Blinding: double-blind<br>Trial completion: 1011/1294 (78%) (Two participants withdrew before receiving drug.) |

**Delmas 2008a** *(Continued)*

| | |
|---|---|
| | Risedronate 5 mg/day: 498/642 (78%)<br><br>Risedronate 150 mg/month: 513/650 (80%) |
| Participants | Inclusion criteria: were at least 50 years of age, ambulatory, in generally good health, postmenopausal (≧ 5 years since last menses), had at least 3 vertebral bodies in the lumbar spine (L1 to L4) that were evaluable by densitometry (i.e. without fracture or degenerative disease), and had a lumbar spine BMD corresponding to a T-score of <−2.5 or a T-score of <−2.0 with at least one prevalent vertebral fracture (T4 to L4).<br><br>Exclusion criteria: any previous or ongoing condition that the investigator judged could prevent the patient from being able to complete the study, drug or alcohol abuse, conditions that would interfere with the BMD measurements, bilateral hip prostheses, history of cancer in the last 5 years excluding basal or squamous skin cancers or successfully treated cervical cancer in situ, body mass index greater than 32 kg/m$^2$, allergy to bisphosphonates, use of medications that could interfere with the study evaluations (e.g. glucocorticosteroids, anabolic steroids, estrogens, selective oestrogen receptor modulators, calcitonin, any bisphosphonates, fluoride, strontium, PTH), abnormal clinical laboratory measurements, creatinine clearance less than 30 ml/min, hypo- or hypercalcaemia, history of hyperparathyroidism or hyperthyroidism unless corrected, osteomalacia, and lumbar spine BMD corresponding to a T-score of ≦−5.<br><br>Age: 64.9 (7.5) years<br><br>Time since menopause: 302 (23.4%) participants 5-10 years; 990 (76.6%) participants ≧ 10 years<br><br>BMI: NR<br><br>Lumbar spine BMD: 0.75 (0.07) g/cm$^2$, femoral neck BMD: 0.73 (0.10) g/cm$^2$<br><br>Lumbar spine T-score: -3.15 (0.57), femoral neck T-score: -1.79 (0.78)<br><br>Prevalent vertebral fractures: 374/1292 (29%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: Argentina, Australia, Belgium, Brazil, Canada, Estonia, Finland, France, Hungary, Lebanon, Norway, Poland, Spain, United States<br><br>Race: Caucasian (94%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Risedronate 150 once monthly: A single 150 mg tablet on the same calendar day each month, followed by a similar placebo tablet daily for the rest of the month<br><br>(All participants received daily calcium 1000 mg and Vitamin D 400-500 IU, the maximal was allowed to 1000 IU/day.) |
| Outcomes | Fractures were assessed and evaluated as adverse events.<br><br>Radiographic vertebral fractures: assessed by semi-quantitative analysis of lateral thoracic and lumbar spine radiographs collected at screening and after 12 months. Radiographs were reviewed for quality and analysed for fracture at a central site (Synarc, Copenhagen/Hamburg).<br><br>Non-vertebral, clinical vertebral, hip and wrist fractures, withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, atypical femoral fractures, acute phase reactions and osteonecrosis of the jaw: Participant's safety was monitored through the study and events were reported as adverse events. |
| Notes | 1. Funded by the Alliance for Better Bone Health (Procter and Gamble Pharmaceuticals, Inc. and Sanofi-Aventis US Inc.) |

**Delmas 2008a** *(Continued)*

2. Trial Registry Number: NCT00247273

3. Two arms have the same monthly dose so no pair-wise comparison data were available after arms being combined. Detailed comparisons were summarized in Table 2, Appendix 5.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomized, double-blind, active-controlled, parallel-group study; eligible patients who gave consent were randomly assigned in a 1:1 ratio to the 2 treatment groups."<br><br>Method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | "Patients received oral risedronate 5 mg daily or 150 mg once a month (i.e. a single 150 mg tablet on the same calendar day each month, followed by a placebo tablet daily for the rest of the month). All tablets were identical in appearance and supplied in identical blister cards."<br><br>Blinding approach was appropriate. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding approach was appropriate to avoid bias in the assessment for objective outcomes. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Blinding approach was appropriate to avoid bias in the assessment for subjective outcomes. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | All the fracture outcomes were assessed as safety outcomes. The statistical methods was not provided. However, the completion rate was 538/652 (84%) in the 5 mg daily group and 556/650 (86%) in the monthly group. The reasons and numbers of the early discontinuations were balanced across groups. It was judged to be at low risk of bias. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Six safety outcomes, including withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, atypical femoral fractures, acute phase reactions and osteonecrosis of the jaw, were reported. As above, it was judged to be at low risk of bias given the reasonable and balanced attrition across groups. |
| Selective reporting (reporting bias) | Low risk | The outcomes were reported as planned in the registered protocol (NCT00247273) and method section in the publication. |
| Other bias | Low risk | No other source of bias was detected. |

**Delmas 2008b**

***Study characteristics***

| | |
|---|---|
| Methods | Randomised controlled trial<br><br>Secondary prevention |

**Delmas 2008b** *(Continued)*

| | |
|---|---|
| | Duration: 24 months<br><br>Blinding: double-blind<br><br>Trial completion: 941/1229 (77%)<br><br>Risedronate 5 mg/day: 467/613 (76%)<br><br>Risedronate 150 mg/month: 474/616 (77%) |
| Participants | Inclusion criteria: healthy, ambulatory women if they were at least 50 years old and were post-menopausal for ≧ 5 years; have osteoporosis as defined by lumbar spine T-scores of < 2.5 SD below the mean value in normal young women, and < 2.0 SD below the mean value in normal young women for subjects having at least one prevalent vertebral fracture.<br><br>Exclusion criteria: If they have received any bone active drugs within 3 months of the first dose of the study medication, if they had drug or alcohol abuse, or if they had a body mass index > 32 kg/m$^2$.<br><br>Age: 64.7 (7.78) years<br><br>Time since menopause: 17.8 (8.8) years<br><br>BMI: NR<br><br>Lumbar spine BMD: 0.75 (0.07) g/cm$^2$, femoral neck: 0.61 (0.08) g/cm$^2$<br><br>Lumbar spine T-score: -3.17 (0.55), femoral neck T-score: -2.07 (0.63)<br><br>Prevalent vertebral fractures: NR/1229 (approximately 30%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: Argentina, Australia, Canada, the Czech Republic, Franc, Lebanon, Poland, South Africa, Turkey, UK, and USA.<br><br>Race: NR |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Risedronate 150 mg/month: 75 mg risedronate on two consecutive days each month (2CDM)<br><br>(All participants received daily calcium 1000 mg and Vitamin D 400-800 IU.) |
| Outcomes | Fractures were assessed and evaluated as adverse events.<br><br>Radiographic vertebral fractures: anterior/posterior and lateral X-rays of the lumbar spine, lateral X-rays of the thoracic spine, and dual energy X-ray absorptiometry (DXA) were obtained before treatment initiation. New vertebral fractures was determined on the comparison of X-ray measurements from baseline to month 12 and 24.<br><br>Non-vertebral, clinical vertebral,withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, atypical femoral fractures, acute phase reactions and osteonecrosis of the jaw: Participant's safety was monitored through the study and events were reported as adverse events. |
| Notes | 1. Funded by Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA, and Sanofi-Aventis, Paris, France).<br><br>2. Trial Registry Number: NCT00358176<br><br>3. Two arms have the same monthly dose so no pair-wise comparison data were available after arms being combined. Detailed comparisons were summarised in Table 2, Appendix 5. |

**Delmas 2008b** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised, multicentre, double-blind, active-controlled, parallel-group study. Participants were randomly assigned at a 1:1 ratio to one of two risedronate oral dosing regimens, 75 mg 2CDM, or 5 mg dosed daily. |
| Allocation concealment (selection bias) | Unclear risk | The method allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Unclear risk | Participants were randomly assigned at a 1:1 ratio to one of two risedronate oral dosing regimens, 75 mg 2CDM, or 5 mg dosed daily.<br><br>Blinding approach was not provided. Although both were the same drug (active ingredients), they involved different dose schedules. It was not clear whether participants' and personnel' performance would likely been influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding approach was not provided in the abstract. However, it was judged to be low risk of bias given that the assessment of objective outcomes were based on objective e and clinical criteria which were less likely biased. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | As above, it was not clear if the blinding was effective to prevent the participants, investigators, and assessors knowing the allocated interventions after assignment. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Quote: "The primary analysis population was all subjects who were randomised, received at least one dose of study drug, and had evaluable measurements of lumbar spine BMD at both baseline and month 12. The results were confirmed by analysis of the PP and ITT populations, which showed non-inferior."<br><br>Fractures reported as adverse events of special interest. Total completion rate was 538/652 (84%) in the 5 mg daily group and 556/650 (86%) in the monthly group. The impact from the attrition was likely modest. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | The risk of withdrawals due to adverse events was 9% in the daily group and 8% in the monthly group which was balanced. The analysis population (safety) was highly representative of randomised participants (99.8%). Given the modest attrition described above, it was judged to be at low risk of bias. |
| Selective reporting (reporting bias) | Low risk | Reported as planned in the NCT00358176 protocol and method section of the parent study. |
| Other bias | Low risk | No other source of bias. |

**Dobnig 2006**

***Study characteristics***

| | |
|---|---|
| Methods | Randomised and placebo-controlled trial<br><br>Secondary prevention<br><br>Duration: 12 months |

**Dobnig 2006** *(Continued)*

| | |
|---|---|
| | Blinding: NR<br><br>Trial completion: 56/61 (92%)<br><br>Bisphosphonate: 37/41 (90%) (risedronate: 19/21 or alendronate: 18/20)<br><br>Control: 19/20 (95%) |
| Participants | Inclusion criteria: postmenopausal women older than 60 who fulfilled criteria for osteoporosis according to WHO guidelines and had a bone mineral density T-score of <-2.5 SD at the femoral neck.<br><br>Exclusion criteria: women with a history of renal or gastrointestinal disease, active malignancy, hyperthyroidism or hyperparathyroidism were excluded from the study. Patients using bisphosphonates (BP), hormone replacement therapy, calcitonin, fluorides, anabolic drugs or calcitriol within the year prior to study enrolment or on medications known to affect bone metabolism (e.g. anticonvulsants, statins, glucocorticoids).<br><br>Age: 68.0 (5.3) years<br><br>Time since menopause: NR<br><br>BMI: 24.2 (2.3) kg/$m^2$<br><br>Lumbar spine BMD: NR, femoral neck BMD: -0.95 (0.17) g/$cm^2$<br><br>Lumbar spine T-score: NR, femoral neck T-score: NR<br><br>Prevalent vertebral fractures: 19/56 (34%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: Germany<br><br>Race: NR |
| Interventions | Two-arm comparison:<br><br>1. Bisphosphonate (risedronate 5 mg/day or alendronate 10 mg/day)<br><br>2. Control: No treatment<br><br>(All participants received daily calcium 1000 mg to 1200 mg, and Vitamin D 400 IU to 800 IU.) |
| Outcomes | None of the fracture outcome of interest was reported.<br><br>One safety outcome, withdrawals due to adverse events, was reported but the ascertainment was not specified. |
| Notes | Funding information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "All study subjects were randomised (using the permuted block method with a block size of four patients per block) to receive daily oral BP treatment."<br>The method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | The method for allocation concealment was not provided. |

**Dobnig 2006** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias) | High risk | It was an open-labelled study and the participants assigned to control group probably did not take any medication or placebo. Also in the treated arm, either risedronate or alendronate was used. The participants' and personnel' performance would likely been influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the objective outcomes of interest were extracted. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | As above, it is an open-labelled study where the assessment of subjective outcomes would likely biased if blinding was not performed. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Only one safety outcome, withdrawals due to adverse events, was reported, with which all randomised participants were included. |
| 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 | Quote: "All study subjects were randomised (using the permuted block method with a block size of four patients per block) to receive daily oral BP treatment."<br><br>The participants were only randomised to control and bisphosphonate groups. Participants in the latter group, nevertheless, would receive alendronate or risedronate but no further information was provided. It was not clear if it was free from other bias. |

**Dundar 2009**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised controlled trial<br><br>Secondary prevention<br><br>Duration: one year<br><br>Blinding: NR<br><br>Trial completion: 61/61 (100%)<br><br>Risedronate: 41/41 (100%)<br><br>No treatment: 20/20 (100%) |
| Participants | Inclusion criteria: postmenopausal women who fulfilled criteria for osteoporosis according to WHO guidelines and had a bone mineral density T-score of ≤ 2.5 SD.<br><br>Exclusion criteria: patients with a history of renal or gastrointestinal disease, active malignancy, thyroid disease, or parathyroid disease. Patients using anti-osteoporotic treatment (bisphosphonates, hormone replacement therapy, calcitonin, fluorides, anabolic drugs or calcitriol), or on medications known to affect bone metabolism (e.g. anticonvulsants, statins, glucocorticoids). |

**Dundar 2009** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: postmenopausal women who fulfilled criteria for osteoporosis according to WHO guidelines and had a bone mineral density T-score of ≤ 2.5 SD.<br><br>Age: 60.3 (9.0) years<br><br>Time since menopause: NR<br><br>BMI: 25.1 (2.3) kg/$m^2$<br><br>Lumbar spine BMD: 0.81 (0.08) g/$cm^2$, femoral neck BMD: 0.82 (0.10) g/$cm^2$<br><br>Lumbar spine T-score: NR, femoral neck T-score: NR<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: 61/61 (100%)<br><br>Source: Turkey<br><br>Race: NR |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 35 mg once weekly<br><br>2) Control: No treatment<br><br>(All participants received daily calcium 1000 mg and vitamin D 400 IU.) |
| Outcomes | None of the fracture outcomes of interest were reported.<br><br>Withdrawals due to adverse events:assessment methods were not described. |
| Notes | Funding information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Quote: "Patients were randomly divided in two groups. Every first and second person on a list of names (n = 61) were assigned to the treatment group and every third person to the control group. The sequence of names on the list was ordered according to time and date of recruitment."<br><br>The sequence was generated by time and date of recruitment, which was not at random. |
| Allocation concealment (selection bias) | High risk | The method for 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 | Blinding was not mentioned and probably an open-label study due to the treatment of two groups were different (risedronate versus no treatment). The participants' and personnel' performance would likely been influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the objective outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Blinding was not mentioned and probably an open label study due to the treatment of two groups were different. However, only the outcome of "with- |

**Dundar 2009** *(Continued)*

| | | |
|---|---|---|
| | | drawal due to adverse events" was extracted and there was no early discontinuation in both groups. It was judged to be at low risk of bias. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Quote: "All patients completed the study."<br>There was no attrition bias. |
| Selective reporting (reporting bias) | Low risk | No safety outcomes were mentioned in the method section. |
| Other bias | Low risk | It appears to be free of other risks of bias. |

**Fogelman 2000**

| ***Study characteristics*** | |
|---|---|
| Methods | Multinational, randomised controlled trial<br>Secondary prevention<br>Duration: two years (The 2.5-mg risedronate group was discontinued by protocol amendment at 9 of the 13 centres, on the basis of efficacy and safety assessments from other RCTs)<br>Blinding: double-blind<br>Trial completion: 355/543 (65%)<br>Risedronate 5 mg/day: 143/180 (79%)<br>Risedronate 2.5 mg/day: 73/184 (40%)<br>Placebo: 139/179 (78%) |
| Participants | Inclusion criteria: women up to 80 years who had been postmenopausal at least 1 year. Mean lumbar T-score of -2 or less.<br>Exclusion criteria: hyperthyroidism, hyperparathyroidism, or osteomalacia within 1 year; a history of cancer or abnormalities affecting lumbar BMD measurement; having taken or still taking drugs or treatments within 6 - 12 months affecting bone metabolism including parenteral Vitamin D = 10,000 IU.<br>Age: 64.7 (7.2) years<br>Time since menopause:17.7 (8.6) years<br>BMI: 25.1 kg/m$^2$<br>Lumbar spine BMD: 0.74 (0.08) g/cm$^2$, femoral neck BMD: 0.63 (0.09) g/cm$^2$<br>Lumbar spine T-score: -2.90 (0.70), femoral neck T-score: NR<br>Prevalent vertebral fractures: 155 (29%)<br>Previous bisphosphonate experience: NR<br>Source: France, UK, the Netherlands, Belgium, and Germany. |

**Fogelman 2000** *(Continued)*

| | |
|---|---|
| | Race: NR |
| Interventions | Three-arm comparison:<br>1. Risedronate 5 mg/day<br>2. Risedronate 2.5 mg/day<br>3. Placebo<br>(All participants received daily calcium 1000 mg.) |
| Outcomes | Fractures were assessed and evaluated as adverse events.<br>Radiographic vertebral fractures: assessed from thoracic and lumbar (T4–L4) lateral and anterior-posterior spinal radiographs taken at baseline, and from lateral spinal radiographs taken at the end of the study. Potential fractures were identified by quantitative morphometry, and subsequent visual verification of fractures was performed by a qualified radiologist. A vertebral body was considered to be fractured if any of the vertebral height ratios fell below 3 standard deviation of the mean for the study population.<br>Non-vertebral fractures: ascertainment was not specified.<br>Withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events: evaluated by assessment of adverse events. |
| Notes | 1. Funded by Procter & Gamble Pharmaceuticals and Aventis Pharmaceuticals.<br>2. The 2.5-mg risedronate group was discontinued by protocol amendment at 9 of the 13 centres, 76 patients, on the basis of efficacy and safety assessments from other randomised, placebo-controlled clinical trials. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "were randomised"; "within each centre, the randomisation was stratified according to the time since menopause (5 yr or less, or more than 5 yr)"<br>Method for sequence generation was not described in detail. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | High risk | This was a double-blind study, but the blinding methods were not provided. Similarity of treatments was not reported and the early withdrawal of most participants from the 2.5 mg group may have broken the blinding of other participants. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "Potential fractures were identified by quantitative morphometry, according to the guidelines of the US National Osteoporosis Foundation Working Group on Vertebral Fractures (30), and subsequent visual verification of incident fractures was performed by a qualified radiologist."<br>Outcome assessors was likely blinded. In addition, other objective outcomes, including non-vertebral fracture, was unlikely to be affected. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | This was a double-blind study, but the blinding methods were not provided. Similarity of treatments was not reported and the early withdrawal of most participants from the 2.5 mg group may have broken the blinding of other par- |

**Fogelman 2000** *(Continued)*

| | | |
|---|---|---|
| | | ticipants. Therefore, we judged subjective outcomes to be at a high risk of detection bias. |
| Incomplete outcome data (attrition bias)<br>Efficacy outcomes | High risk | Quote: "A total of 543 women were enrolled in the study: 180 were randomised to receive placebo; 184, risedronate (2.5 mg); and 179, risedronate (5 mg). Two patients in the 5-mg risedronate group were excluded from the intention-to-treat analysis because they did not receive study medication...A total of 355 patients completed 24 months of treatment: 143 in the placebo group, 73 in the risedronate 2.5-mg group, and 139 in the 5-mg risedronate group."<br><br>Fractures were reported as safety events. Two-year overall completion rate was 65.4% (355/543) , which was less than 80%, and probably introduce significant amount of bias. |
| Incomplete outcome data (attrition bias)<br>Safety Outcomes | High risk | As above, the effect size estimates of safety outcome, including serious adverse events, withdrawals due to adverse events and gastrointestinal adverse events, may be biased by the high attrition. |
| Selective reporting (reporting bias) | Low risk | No protocol or NCT record was found. However, the methods/abstract and results section described the same outcomes. |
| Other bias | Unclear risk | The 2.5-mg risedronate group was discontinued by protocol amendment at 9 of the 13 centres, on the basis of efficacy and safety assessments from other RCTs. It was not clear whether and what kind of bias would have been introduced by the change. |

**Fukunaga 2002**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: 48 weeks<br><br>Blinding: double-masked, double-dummy<br><br>Trial completion: 200/235 (85%)<br><br>Risedronate: 98/118 (83%)<br><br>Etidronate: 102/117 (87%) |
| 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.<br><br>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 interfered with accurate L2-L4 BMD determination, e.g. severe spinal scoliosis, fracture, deformity or osteosclerotic change in L2-L4.<br><br>Age: 62.6 (6.2) years<br><br>Time since menopause: 13.3 (7.2) years<br><br>BMI: 21.4 (2.8) kg/$m^2$ |

**Fukunaga 2002** *(Continued)*

| | |
|---|---|
| | Lumbar spine BMD: 0.66 (0.08) g/cm$^2$, femoral neck: NR<br><br>Lumbar spine T-score: -2.97 (0.44), femoral neck T-score: NR<br><br>Prevalent vertebral fractures: 34 (14.5%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: France, the UK, the Netherlands, Belgium, and Germany.<br><br>Race: Asian (100%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 2.5 mg/day<br><br>2. Etidronate 200 mg/day: four cycles of 2 weeks of treatment with etidronate 200 mg/day followed by 10-week medication-free periods.<br><br>(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.<br><br>Non-vertebral fractures, withdrawals due to adverse events, and gastrointestinal adverse events: ascertainment was not specified and evaluated by the assessment of adverse events. |
| Notes | 1. Funded by a grant from the Joint Development Program of Ajinomoto Co., Inc., Aventis Pharma Ltd and Takeda Chemical Industries Ltd.<br><br>2. Two men included in this study were reduced from the denominator to meet the PICO eligibility of this review while any reported fracture could be used for female. Data for non-vertebral fractures were not used in the analysis because the data might have included male subject. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "In this multicenter, randomised, double-masked, active (etidronate) controlled comparative study". 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) | 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...Risedronate and its placebo tablets were supplied by Takeda Chemical Industries (Osaka, Japan), and etidronate and its placebo tablets by Sumitomo Pharmaceuticals (Tokyo, Japan).<br><br>The approaches were judged sufficient to blind the participants and personnel. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | In addition to the double-dummy techniques, Quote: " ...Lateral and anteroposterior thoracic and lumbar spine radiographs were obtained at baseline and after treatment, and vertebral fractures were evaluated according to the previously mentioned diagnostic criteria. " |

**Fukunaga 2002** *(Continued)*

| | | |
|---|---|---|
| | | The assessment of the objective outcomes were less likely biased. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding approaches were appropriate so the assessment of the subjective outcomes were less likely biased. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Quote: "Efficacy of the drug was evaluated for the patients who received study medication for 24 weeks or more and with available data on L2–L4 BMD (risedronate: 102, etidronate: 107). " In this 48-week trial, 89% (209/235) of randomised participants were included in the efficacy analysis. Among them, 83% (98/118) in risedronate group and 87% (102/117) in etidronate group complete the study. The number and reasons for the early discontinuations were evenly distributed. It is judged to be low risk of bias given that the completion rates in each group all exceeded 80%. The portion of missing data would less likely to bias the outcome estimate. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Quote: "Safety of the drug was evaluated for the patients who were randomised to receive any study medication (risedronate: 118, etidronate: 117)". All randomised participants were included in the safety analysis. It is also judged to be low risk of bias given that the completion rates in each group all exceeded 80%. The portion of missing data would less likely to bias the 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 appeared to be free of other risks of bias. |

**Galesanu 2011**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br>Secondary prevention<br>Duration: three years<br>Blinding: NR<br>Trial completion: NR/198<br>Risedronate: NR/32<br>Alendronate: NR/133<br>Ibandronate: NR/33 |
| Participants | Inclusion criteria: 230 postmenopausal women with osteoporosis. The diagnosis was based by WHO criteria using DXA-BMD.<br>Exclusion criteria: NR<br>Age: 63.3 (3.1) years<br>Time since menopause: 16.1 (1.1) years<br>BMI: NR<br>Lumbar spine BMD: 0.74 g/cm$^2$, femoral neck BMD: NR |

**Galesanu 2011** *(Continued)*

| | |
|---|---|
| | Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: NR<br>Source: Romania<br>Race: NR |
| Interventions | Three-arm comparison:<br>1. Risedronate 35 mg once weekly<br>2. Alendronate 70 mg once weekly<br>3. Ibandronate 150 mg once monthly<br>(Background medication was not reported.) |
| Outcomes | Fracture outcomes were assessed as adverse events, and inferred zero from the abstract text, including clinical vertebral, non-vertebral, hip, wrist and atypical femoral fractures. The ascertainment was not specified.<br>None of other safety outcomes of interest were reported. |
| Notes | 1. Funding information: NR<br>2. This was a poster presentation abstract (1st Middle-East & Africa Osteoporosis Meeting) with efficacy and safety data briefly reported. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: “The patients were randomised 3/1/1 and they were treated with alendronate 70 mg/weekly, 133 cases; risedronate 35 mg/weekly, 32 cases and Ibandronate 150 mg/month, 33 cases.”<br>However, the method for sequence generation was not provided in the abstract. |
| Allocation concealment (selection bias) | Unclear risk | As above, the method for allocation concealment was not provided in the abstract. |
| Blinding of participants and personnel (performance bias) | High risk | Blinding was not mentioned in the abstract. It was likely open-labelled because three bisphosphonates involved two different dose regimens (weekly versus monthly). The differences in-between treatments would likely influence the participants' and personnel' performance. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Although it was likely an open-labelled study, the assessment of fracture outcomes was based on objective and clinical evidence, which were less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | None of the subjective outcomes of interest were reported. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | This was a 3-year study where fracture was reported as an adverse event and inferred from Quote: "No new fractures under the treatment in our patients.". |

**Galesanu 2011** *(Continued)*

| | | |
|---|---|---|
| | | Relevant information, including statistical analysis methods and attrition were not provided in the abstract. It was judged as unclear risk of bias. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | Only one safety outcome, atypical femoral fracture, was inferred from Quote: "No new fractures under the treatment in our patients." There was no other safety outcome of interest was reported in the abstract. Relevant information, including statistical analysis methods and attrition were not provided in the abstract. It was judged as unclear risk of bias. |
| Selective reporting (reporting bias) | Unclear risk | No relevant information was provided in the abstract. |
| Other bias | Unclear risk | Data were inferred from the abstract. It is not clear if any important bias would have been introduced. |

**Gu 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised controlled trial<br><br>Primary prevention<br><br>Duration: one year<br><br>Blinding: double-blind<br><br>Trial completion: NR/290<br><br>Risedronate 35 mg once weekly: NR/145<br><br>Risedronate 5 mg/day: NR/145 |
| Participants | Inclusion criteria: women 50 and 80 years of age, ambulatory, in generally good health, and postmenopausal (at least 1 year since last menses). Their body mass indices (BMIs) were between 18 and 30. They had no severe lumbar anatomical abnormalities that could affect DXA bone densitometry, such as severe scoliosis. BMD inclusion criteria were the following. (1) Osteopenia (a femoral neck, lumbar spine 1–4, or total hip BMD T-score between -1 and -2.5SD). They also had to meet at least one of the following two risk factors: advanced age (≥ 65 years) or more than 10 years since the last menses. The number of cases of osteopenia comprised one-third of the total number of patients. (2) Osteoporosis: a femoral neck, lumbar spine 1–4, or total hip BMD T-score of less than -2.5; a T-score of less than -1.0 at any of the three sites above and with at least one fragility fracture. If lumbar spine 1–4 fractures were present, BMD was calculated from the mean of the two adjacent, unfractured vertebral bones.<br><br>Exclusion criteria: had serious heart disease (such as myocardial infarction, unstable angina pectoris, cardiac insufficiency, severe arrhythmia; or serious gastrointestinal diseases (such as reflux oesophagitis or peptic ulcer, were excluded); a history of diabetes uncontrolled with medications and fasting blood glucose >7.0 mmol/L; serious organic diseases of the nervous and endocrine systems; disorders of the bones and joints, and other chronic diseases were disqualifiers; high blood pressure >160/95 mmHg, even with antihypertensive drugs; liver enzyme levels 1.5 times the upper limits of normal for serum alanine transaminase (ALT) or serum aspartate aminotransferase (AST); serum creatinine >133 µmol/L; white blood cell count <3.5×109 /L, or haemoglobin <100 g/L; participants who had used bisphosphonates, fluoride, or glucocorticoids in the preceding 12 months; oestrogen, calcitonin, ipriflavone, selective oestrogen receptor modulators, strontium salt, or active vitamin D in the preceding 6 months; Xianlinggubao, Gusongkang, or Qianggujiaonang in the preceding 3 months; or were allergic to bisphosphonates.<br><br>Age: 63.0 (6.8) years |

**Gu 2015** *(Continued)*

| | |
|---|---|
| | Time since menopause: 14.0 (5.4) years<br>BMI: 23.6 (3.0) kg/m$^2$<br>Lumbar spine BMD: 0.79 (0.12) g/cm$^2$, femoral neck BMD: 0.68 (0.10) g/cm$^2$<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: NR<br>Source: China<br>Race: Asian (100%) |
| Interventions | Two-arm comparison:<br>1. Risedronate 35 mg once weekly (orally)<br>2. Risedronate 5 mg/day (orally)<br>(All participants received daily calcium 500 mg and vitamin D 200 IU.) |
| Outcomes | Fractures were assessed and evaluated as adverse events.<br>Radiographic vertebral fractures: lateral thoracic and lumbar spine radiographs were collected at screening and at 0 and 12 months and were then analysed for vertebral fractures by semi-quantitative analysis.<br>Non-vertebral,hip, wrist, clinical vertebral, atypical femoral fractures, withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events and osteonecrosis of the jaw: Assessment methods were not described and events were monitored and reported as adverse events. |
| Notes | 1. Funded by Kunming Jida Pharmaceutical Co, Ltd, Kunming, China.<br>2. Two arms have the same weekly dose so no pair-wise comparison data were available after arms being combined. Details in Table 2, Appendix 5. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "All subjects, in accordance with the table generated by software, were randomly assigned to the experimental group (35 mg of oral risedronate once a week) or control group (5 mg of oral risedronate daily)." |
| Allocation concealment (selection bias) | Unclear risk | Method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "The weekly-group members took a single 35-mg tablet on the same calendar day each week and a placebo tablet daily; the daily-group members took a 5-mg tablet daily and a placebo tablet on the same calendar day each week; all the tablets were identical in appearance."<br>Blinding approach was appropriate. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding methods were appropriate, and the assessment for objective outcomes was less likely influenced. |

**Gu 2015** *(Continued)*

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|---|---|---|
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding methods were appropriate, and the assessment for subjective outcomes was less likely influenced. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Fractures were reported as safety events. Total withdrawals did not seem to be reported, but per protocol set analysis included 119/145 (82%) of the weekly group and 115/144 (80%) of the daily groups. Total completion rate was expected to be at least as much as the per protocol set, thus overall considered low ROB although total withdrawal was not clearly reported. Additionally, withdrawals due to AEs were 10/145 (7%) in weekly and 8/144 (6%) in daily groups, which were quite similar. Denominators for safety analysis were provided, population was very representative of all randomised participants (289/290). |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | As above, it was judged to be at low risk of bias. |
| Selective reporting (reporting bias) | Low risk | It was the same as planned in the method section. No other data to compare. |
| Other bias | Low risk | No other sources of bias were observed. |

**Hadji 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br>Secondary prevention<br>Duration: 18 months<br>Blinding: double-blind, double-dummy<br>Trial completion: 528/710 (74%)<br>Risedronate: 269/350 (77%)<br>Teriparatide: 259/360 (72%) |
| Participants | Inclusion criteria: women ≥45 years of age at least 2 years postmenopausal, and had a history of back pain for ≥2 months before screening that was likely, in the opinion of the investigator, to be caused by osteoporotic vertebral fracture, despite conservative analgesic treatment; a baseline mean pain score of at least 4.0 on the numeric rating scale during the week before randomisation; lumbar spine, femoral neck, or total hip bone mineral density (BMD) T-score of ≤−2; and a minimum of one moderate vertebral fracture.<br>Exclusion criteria: any diseases affecting bone metabolism other than osteoporosis; elevated serum calcium values, abnormal serum thyroid-stimulating hormone, parathyroid hormone, or 25-hydroxyvitamin D levels; imminent need for kyphoplasty or vertebroplasty; and evidence of significant pathology related to back pain which would make the interpretation of the back pain related to an osteoporotic vertebral fracture difficult, based on investigator assessment.<br>Age: 71.0 (8.5) years<br>Time since menopause: NR<br>BMI: 26.3 (4.9) kg/$m^2$ |

**Hadji 2012** *(Continued)*

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|---|---|
| | Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: -2.66 (1.15), femoral neck T-score: -2.38 (0.71)<br>Prevalent vertebral fractures: 710/710 (100%)<br>Previous bisphosphonate experience: NR<br>Source: USA, Argentina, Brazil<br>Race: Caucasian (80.4%), Asian (0.4%), Black/African-American (0.7%) |
| Interventions | Two-arm comparison:<br>1. Risedronate 35 mg once weekly + placebo (of Teriparatide), SC daily<br>2. Teriparatide 20 µg/day, SC + placebo (of Risedronate) once weekly<br>(All participants received daily calcium 1000 mg and vitamin D 800 IU.) |
| Outcomes | Fractures were assessed and evaluated as adverse events.<br>Radiographic vertebral fractures: Incident and severity of new and new or worsening vertebral fractures from baseline to 6 and 18 months with spine radiographs assessed by a central reader (BioClinica; Newton, PA) blinded to treatment assignment using semi-quantitative analysis.<br>Non-vertebral, hip and wrist fractures: assessed by the investigator, ascertainment not specified.<br>Health-related quality of life: assessed by Quality of Life Questionnaire of the European Foundation for Osteoporosis.<br>Withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, and atrial fibrillation: Assessment methods were not described and events were monitored and reported as adverse events. |
| Notes | 1. Funded by Eli Lilly and Company.<br>2. Trial Registry Number: NCT00343252. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "This was an 18-month, randomised, parallel, double-blind, double-dummy, active-controlled trial comparing the effects of teriparatide (Forteo®, Eli Lilly and Co.) to risedronate"<br>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 | Quote: "Subjects were randomly assigned to receive daily teriparatide 20 µg sc. injections plus placebo tablet orally once weekly or daily placebo sc. injections plus risedronate 35 mg orally once weekly."<br>Double-dummy technique was adopted but it was not clear whether the tablet and injection placebo were indifferent from the respective active drugs. It was not clear whether participants and personnel were sufficiently blinded. |

**Hadji 2012** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | It was not clear whether the blinding was sufficient. However, the assessment of fracture outcomes was based on objective and clinical evidence which was less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | As above, it was not clear whether the blinding was sufficient. The assessment of subjective outcomes was possibly influenced. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Fractures were an exploratory endpoint. Completion rate in the risedronate group was 269/350 (77%) and 259/360 (72%) in the teriparatide group. Completion rates were balanced in both groups, although slightly lower than 80%. Reasons to the early discontinuations were similar across groups. The fracture analysis population included all those who received at least 1 dose of study drug, and was very representative (710/712, 99.7%). |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Quote: "Analyses were conducted on data from patients who received at least one dose of study drug. Visit-wise analyses were performed using mixed-effect model repeated measure mode."<br><br>Completion rates were balanced in both groups and th reasons to the early discontinuations were similar. It was judged to be at low risk of bias. |
| Selective reporting (reporting bias) | Low risk | The results were reported as planned in the method section and in the registered protocol (NCT00343252). |
| Other bias | Low risk | No other source of bias was found. |

**Harris 1999**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and placebo-controlled trial<br><br>Secondary prevention<br><br>Duration: three years (The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after the first year. A 2-year extensional period was conducted. )<br><br>Blinding: double-blind<br><br>Trial completion (at three years): 939/2458 (38%)<br><br>Risedronate 2.5 mg/day: 722/817 (88% at 1 year), and 0/817 (0%, all discontinued due to protocol amendment)<br><br>Risedronate 5 mg/day: 489/821 (60%)<br><br>Placebo: 450/820 (55%) |
| Participants | Inclusion criteria: ambulatory women up to 85 years old who had been natural or surgical menopausal at least 5 years. Minimum two radiographically confirmed vertebral T4-L4 fractures (ratio of anterior or middle vertebral height to the posterior height was = 0.8) or 1 vertebral fracture and lumbar BMD T-score = -2 SD of young adults (0.83g/cm$^2$ Hologic or 0.94g/cm$^2$ Lunar).<br><br>Exclusion criteria: conditions that could interfere with evaluation of spinal osteoporosis; received calcitonin, calcitriol or Vitamin D within one month prior to study entry, anabolic steroids, or oestrogen or oestrogen-related drugs, or progestins within 3 months, bisphosphonates, fluoride or subcutaneous oestrogen implants within 6 months. |

**Harris 1999** *(Continued)*

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|---|---|
| | Age: 68.7 (0.3) years<br><br>Time since menopause: 24.0 (5.8) years<br><br>BMI: NR<br><br>Lumbar spine BMD: 0.83 (0.09) g/cm$^2$, femoral neck BMD: 0.60 (0.09) g/cm$^2$<br><br>Lumbar spine T-score: -2.4 (0.81), femoral neck T-score: -2.6 (0.64)<br><br>Prevalent vertebral fractures: 1965/2458 (80%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: North America<br><br>Race: Caucasian (96%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 2.5 mg/day<br><br>2. Risedronate 5 mg/day<br><br>3. Placebo<br><br>[All participants received daily calcium 1000 mg; participants with low serum 25-hydroxyvitamin D level at baseline (< 40 nmol/L) also received cholecalciferol up to 500 IU/day.] |
| Outcomes | All fracture endpoints were reported as efficacy outcomes.<br><br>Radiographic vertebralfFractures: Lateral thoraco-lumbar T4-L4 spine radiographs were obtained at baseline and annually. Prevalent and incident fractures were diagnosed quantitatively and semi-quantitatively. Quantitative assessment defined an incident fracture as a 15% decrease of anterior, posterior or middle vertebral height in a vertebra that was normal at baseline. In the semi-quantitative assessment a new fracture was diagnosed if the grade changed from 0 (normal) to 1(mild) 2 (moderate), or 3 (severe). An independent radiologist adjudicated discrepancies between methods. Radiologists were blinded.<br><br>Non-vertebral and wrist fractures: Radiographically confirmed non vertebral fractures (defined as fractures of the clavicle, humerus, wrist, pelvis, hip, or leg, whether or not associated with trauma) were recorded throughout the study.<br><br>Withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events and atypical femoral fractures: Participants' safety was monitored and reported as adverse events. Endoscopy was performed at the discretion of the investigator in subjects who reported gastrointestinal complaints. |
| Notes | 1. Funded by Procter & Gamble Pharmaceuticals and Hoechst Marion Roussel.<br><br>2. Due to the protocol amendment, risedronate 2.5 mg/day arm was discontinued at 1 year. Data for 2.5 mg/day arm was only available for the fracture outcome at the first year.<br><br>3. Outcome data for year four to five were not usable and narratively discussed. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "…randomly assigned (block size of 3 within each stratum at each study centre) to 1 of 3 treatment groups. The randomisation schedule was generated by Quintiles Inc (Durham, NC) using SAS version 6.07 (SAS Inc, Cary, NC)." |

**Harris 1999** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: "During the trial, the randomisation schedule was held by a clinical research organization." |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "…double-blind, placebo-controlled, parallel-group study…" "A number of procedures were in place to maintain blinding throughout the study....Covance staff, the investigators, and other research personnel remained blinded to the treatment assignments…Treatment assignments could be released to the investigators only for reasons of patient safety. To protect the blinding, the placebo and risedronate tablets were physically indistinguishable, and study medication was provided in coded containers labelled with dosing instructions. "<br><br>Multiple approach were used to prevent the participants and personnel from knowing the allocated treatments. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | As above, multiple blinding methods were judged sufficient to avoid detection bias. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, multiple blinding methods were judged sufficient to avoid detection bias. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: "Efficacy analyses were performed on an intention-to-treatment basis… The 2.5-mg risedronate arm was discontinued by protocol amendment after the first year…the data were examined using the last observation carried forward for all patients who withdrew… There were no obvious differences between groups in the reasons for patient withdrawal…"<br>In this 3-year 3-arm study, risedronate 2.5 mg group was discontinued after the first year. It is reported that<br>1-year overall completion rate (CR): 75.7% (1847/2439)<br>2-year overall CR: 55% (450/815) in the placebo group and 60% (489/813) in the risedronate 5 mg group<br>It was judged to be at high risk of bias given the completion rates across the years are less than 80% and the handling of missing data seems inappropriate. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | The statistical methods for safety outcomes of interest were not provided. As reported, the safety analyses (Table 3) include all of the randomised participants. It was judged to be at high risk of bias given the completion rates across the years were less than 80% and the handling of missing data seems inappropriate. |
| 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 2.5 mg risedronate treatment arm was early terminated by protocol amendment. Only the 1-year outcomes data were extracted. However, it was not clear if the early discontinuation of one arm would have introduced bias in other domain. |

**Harris 2001**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Randomised and placebo-controlled trial<br><br>Primary prevention |

**Harris 2001** *(Continued)*

| | |
|---|---|
| | Duration: 12 months<br><br>Blinding: double-blind<br><br>Trial completion: 383/524 (73%)<br><br>Risedronate + HRT: 198/263 (75%)<br><br>Placebo + HRT: 185/261 (71%) |
| Participants | Inclusion criteria: at least 12 months postmenopausal or, if the date of the last menstrual period was uncertain, to have FSH and serum estradiol values within the postmenopausal range. Participants were stratified by duration of menopause (≤ 5 years or > 5 years).<br><br>Exclusion criteria: women who had received HRT for more than 1 month within the past 12 months; recent therapy with drugs known to affect bone turnover evidence of metabolic bone disease, abnormal Pap smear or mammogram, any significant organic or psychiatric disease that could affect participation or interfere with the interpretation of data, and physical characteristics or abnormalities on the anterior/posterior spinal radiographs that could preclude precise dual x-ray absorptiometry (DXA) measurements.<br><br>Age: 58.9 (8.1) years<br><br>Time since menopause: 14.1 (9.8) years<br><br>BMI: NR<br><br>Lumbar spine BMD: 0.97 (0.01) g/cm$^2$, femoral neck BMD: NR<br><br>Lumbar spine T-score: -1.3 (0.13), femoral neck T-score: 0.76 (NR)<br><br>Prevalent vertebral fractures: 149/ 524 (28%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: North America<br><br>Race: NR |
| Interventions | Two-arm comparison:<br><br>1. Risedronate + HRT: Risedronate 5 mg/day plus conjugated equineo estrogens 0.625 mg/day<br><br>2. Placebo + HRT: placebo plus conjugated equine estrogens 0.625 mg/day<br><br>(All participants received daily calcium 1000 mg; patients with 25-hydroxyvitamin D levels below 39.9 nmol/L at screening were supplemented with oral Vitamin D, not exceeding 500 IU/day) |
| Outcomes | All fracture endpoints seemed to be reported as efficacy outcomes.<br><br>Radiographic vertebral fractures: lateral spinal (T4 to L4) were obtained at baseline and 12 months and were analysed. A new (incident) vertebral fracture was defined as a decrease of at least 15% (for intact vertebrae at baseline) or at least 4 mm (for fractured vertebrae at baseline) in any of the measured vertebral heights (anterior, middle, or posterior), which were verified visually by a qualified skeletal radiologist.<br><br>Non-vertebral, hip and wrist fractures: ascertainment not specified.<br><br>Withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events and atypical femoral fractures: Participants' safety was monitored and reported as adverse events. |
| Notes | Funded by a grant from Procter & Gamble Pharmaceuticals (Cincinnati, OH) and Aventis Pharma (Bridgewater, NJ). |

**Harris 2001** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: Patients were randomly assigned to receive either 0.625 mg conjugated equine estrogens plus 5 mg risedronate (263 patients) or 0.625 mg conjugated equine estrogens plus placebo (261 patients) daily for a period of 12 months. " However, 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 | Quote: "This was a double blind, placebo-controlled, parallel group study."<br><br>Blinding approach was not provided. It was not clear whether the participants and personnel were sufficiently blinded. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | It was not clear whether the blinding was sufficient. However, the assessment of fracture outcomes was based on objective and clinical evidence which was less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | A double-blind study but the blinding approach was not provided. It was not clear whether the blinding was sufficient to prevention the participants and outcome assessors from knowing the assigned treatment. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: "Analyses were conducted on the intent to treat population comprised of the randomised patients who took at least one dose of study drug. A total of 524 postmenopausal women were enrolled, of whom 520 received at least 1 dose of study drug (intent to treat population). One hundred and eighty-five women (71%) in the HRT-only group and 198 (76%) in the risedronate-HRT group completed the 12-month study. "<br><br>Except for vertebral fracture, other fracture outcomes were reported as adverse events. The analysis of vertebral fracture only included the participants who have evaluable radiographs. This 12-month study has the completion rates of two groups being less than 80%, and the discontinuation reasons and the handling of missing data were not provided. It was judged to be at high risk of bias. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | As described above, this 12-month study has the completion rates of two groups being less than 80%, and the discontinuation reasons and the handling of missing data were not provided. It was judged to be at high risk of attrition bias for safety outcomes. |
| 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 appears to be free of other risks of bias. |

**Hooper 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and placebo-controlled trial<br><br>Primary prevention |

**Hooper 2005** *(Continued)*

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|---|---|
| | Duration: 2 years<br><br>Blinding: double-masked<br><br>Trial completion: 296/383 (77%)<br><br>Risedronate 2.5 mg/day: 100/128 (79%)<br><br>Risedronate 5 mg/day: 103/129 (80%)<br><br>Placebo: 93/126 (74%) |
| Participants | Inclusion criteria: postmenopausal (as determined from their medical histories) for 6 to 36 months, with a serum follicle stimulating hormone concentration of at least 50 mIU/mL and a serum oestradiol concentration of no more than 20 pg/mL. Menopause could be natural or surgical. Patients who had undergone hysterectomy without bilateral oophorectomy could be enrolled if they were 51 to 60 years of age. All patients were required to have a lumbar spine BMD T-score greater than -2.5 (BMD greater than 0.76 g/cm$^2$ when measured with a Hologic densitometer (Waltham, Massachusetts, USA) or greater than 0.87 g/cm$^2$ when measured with a Lunar densitometer (Madison, Wisconsin, USA)). All patients were in good health and had no history of hyperparathyroidism, hyperthyroidism, or osteomalacia, or of treatment with agents that were likely to affect bone metabolism. Patients were not excluded because of previous or active gastrointestinal disease (including dysphagia, oesophagitis, and oesophageal, gastric, and duodenal ulceration), need for antisecretory therapy, or concomitant use of medications with potential to irritate the gastrointestinal tract.<br><br>Exclusion criteria: NR<br><br>Age: 52.7 (1.8) years<br><br>Time since menopause: 3.9 (2.8) years<br><br>BMI: NR<br><br>Lumbar spine BMD: 1.08 (0.16) g/cm$^2$, femoral neck BMD: 0.77 (0.16) g/cm$^2$<br><br>Lumbar spine T-score: -0.40 (0.17), femoral neck T-score: NR<br><br>Prevalent vertebral fractures: 70/381 (18%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: Australia<br><br>Race: Caucasian (98%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 2.5 mg/day<br><br>2. Risedronate 5 mg/day<br><br>3. Placebo<br><br>(All participants received daily calcium 1000 mg with their midday or evening meal.) |
| Outcomes | Radiographic vertebral and non-vertebral fractures were assessed as adverse events.<br><br>Radiographic vertebral fractures: lumbar and thoracic lateral and anterior-posterior radiographs were taken at baseline and 2 years. Deformity was confirmed by visual inspection and defined as vertebral height ratio below 3 SD of study population mean. Incident fracture was defined as a loss of 14% or more in anterior, posterior or middle vertebral height in a vertebra that was normal at baseline.<br><br>Non-vertebral fractures: ascertainment was not specified. |

**Hooper 2005** *(Continued)*

| | |
|---|---|
| | Withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events: Assessment methods were not described and events were monitored and reported as adverse events. Particular attention was paid to reports of upper gastrointestinal events. |
| Notes | Funded by Procter & Gamble Pharmaceuticals, Cincinnati, Ohio and Sanofi-Aventis, Bridgewater, New Jersey, USA. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients who qualified for the study were randomly assigned in a 1 : 1: 1 ratio to receive placebo or risedronate 2.5 or 5 mg/day, according to a computer-generated randomisation schedule, which was held at the contract research organization." |
| Allocation concealment (selection bias) | Low risk | As above, the randomisation schedule was held by a single centre which was concealed to the study sites. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "…double masked…Patients received 2.5- or 5-mg film-coated risedronate tablets (the commercial dosage form) or matching placebo tablets. All study drugs were provided by Procter & Gamble Pharmaceuticals (Cincinnati, Ohio, USA)..."<br><br>Appropriate methods were adopted to blind the participants and personnel. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | In addition to the above, Quote: "The prevalence and incident of vertebral deformities were assessed by morphometric analysis…Incident deformities were confirmed by visual Inspection."<br><br>The assessment of objective outcomes were not influenced given the appropriate blinding methods and diagnosis criteria. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, matched placebos were provided by the same pharmaceutical company and would be indistinguishable from risedronate. Appropriate methods were adopted to blind the participants and (subjective outcome) assessors. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: “Safety was assessed primarily on the basis of the occurrence of adverse events and vertebral and non-vertebral fractures. Efficacy and tolerability data were analyzed on an intention-to-treat basis. The analyses included all patients who received at least one dose of the study medication.”<br><br>This was a 2-year study and fracture outcomes were reported as adverse events. All the randomised participants included in the analysis, except for 2 not taking the medicine. The 24-month completion rates were 74%, 78% and 80 in placebo, risedronate-2.5 mg and risedronate-5 mg group, respectively. It was judged to be at high risk of bias, given that the overall completion rate was less than 80% and the approaches to handling missing data were not provided. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | As above reasons, the other safety outcomes of interest were judged to be at high risk of attrition bias, given that the overall completion rate was less than 80% and the approaches to handling missing data were not provided. |
| 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 appeared to be free of other risks of bias. |

**Hosking 2003**

| ***Study characteristics*** | |
|---|---|
| Methods | Multi-centre, randomised and placebo-controlled trial<br><br>Secondary prevention<br><br>Duration: 12 months (It was originally a 3-month study with a double-blind extension to 12 months.)<br><br>Blinding: double-blind<br><br>Trial completion: NR/549 (80% at three months)<br><br>Risedronate: NR/222 (79% at three months)<br><br>Alendronate: NR/219 (80% at three months)<br><br>Placebo: NR/108 (82% at three months) |
| Participants | Inclusion criteria: postmenopausal (at least 2 years) women ≥ 60 and ≤ 90 years of age with osteoporosis as defined by low BMD (lumbar spine or total hip BMD T-score ≤ -2.5, or both lumbar spine and total hip BMD T-score ≤ -2.0) were eligible. Patients were required to be in good general health with spinal anatomy suitable for DXA of the lumbar spine.<br><br>Exclusion criteria: a history of any illness or if significant abnormalities that, in the opinion of the investigator, might compromise the patient's safety or the evaluation of the study results; patients with osteoporosis, so severe that (in the judgment of the investigator) participation in a placebo controlled trial was unethical; patients with a baseline 25-hydroxyvitamin D level < 9 ng/mL, or < 15 ng/mL with biochemical evidence of osteomalacia: elevated parathyroid hormone or alkaline phosphatase, or decreased 24-hour urine calcium; with an oesophageal stricture, achalasia, or severe oesophageal motor dysfunction were excluded, while patients with other recent but controlled gastrointestinal mucosal erosive disease were eligible; metabolic and other bone diseases; Prior concomitant medications: oestrogen preparations (> 2 weeks within 6 months), thyroid hormone (for < 6 weeks before the study or with abnormal thyroid stimulating hormone), fluoride (>1 mg/day), glucocorticoids (>1 month within 6 months), bisphosphonate (> 2 weeks), and supplemental calcium (except if ongoing for >4 weeks).<br><br>Age: 69.2 (3.4) years<br><br>Time since menopause: 20.6 (5.1) years<br><br>BMI: 25.1 (3.6) kg/$m^2$<br><br>Lumbar spine BMD: 0.72 (0.23) g/$cm^2$, femoral neck BMD: NR<br><br>Lumbar spine T-score: NR, femoral neck T-score: NR<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: 38 outpatient sites in Europe and Brazil<br><br>Race: Caucasian (99.5%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Alendronate 70 mg once weekly<br><br>3. Placebo |

**Hosking 2003** *(Continued)*

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|---|---|
| | (All participants received daily calcium 1000 mg; Patients with a baseline 25- hydroxy-vitamin D level below 15 ng/mL (without evidence of vitamin D deficiency) received supplementation providing 400 IU/day of vitamin D 400 IU/day.) |
| Outcomes | Fractures were reported but the anatomic location was not provided so they were not included in our analysis.<br><br>Three safety outcomes, withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events, were reported but the ascertainment was not specified. |
| Notes | 1. Funded by Merck & Co., Inc..<br><br>2. A 3-month study with double-blind extensions to 12 months. Data of 12 months was extracted. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: " During the randomisation visit, patients who met all entry criteria were assigned in accordance with a computer-generated, blinded randomisation schedule to one of three treatment groups: ..." |
| Allocation concealment (selection bias) | Low risk | As above, a "blinded randomisation schedule" was used. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "To maintain treatment blinding, patients took both tablet images (from bottles containing either active therapy or placebo) and adhered to both dosing regimens for the entire 12 months on study."<br><br>Blinding approaches were used and appropriate. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the objective outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Blinding approaches were used and appropriate. The assessment of subjective outcomes was less likely influenced. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | From Figure 1, the 3-month completion rates were 78.5%, 80.2% and 82.4%, or overall 80.0%. The completion rate at 12 months was not found. Since more people may discontinue from the study in the last 9 months, it was judged to be at high risk of bias given the overall completion rate might be less than 80%, unclear end-of-trial completion rate, and the lack of the describing the approach to handling missing data. The statistical method for safety outcomes of interest was not provided. However, from table 6, it seemed all randomised participants were included. |
| 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 appears to be free of other risks of bias. |

**Kasukawa 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Blinding: NR<br>Trial completion: 55/101 (55%)<br>Risedronate: 29/50 (58%)<br>Risedronate+ menatetrenone (Vitamin $K_2$): 26/51 (51%) |
| Participants | Inclusion criteria: osteoporotic women aged [60 years were eligible for this study; patients had no history of treatment for osteoporosis, and osteoporosis was defined with a forearm BMD < -2.5 standard deviation (SD) of the T score for Japanese women.<br>Exclusion criteria: recipients of warfarin or steroids, and patients with hyperparathyroidism, hyperthyroidism or chronic renal failure.<br>Age: 74.7 (6.3) years<br>Time since menopause: NR<br>BMI: 23.4 (3.4) $kg/m^2$<br>Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: 43/101 (43%)<br>Previous bisphosphonate experience: 0/101 (0%)<br>Source: Japan<br>Race: Asian (100%) |
| Interventions | Two-arm comparison:<br>1. Risedronate 17.5 mg once weekly<br>2. Risedronate 17.5 mg once weekly + menatetrenone (Vitamin $K_2$) 45 mg/day<br>(No background medication.) |
| Outcomes | Radiographic vertebral fractures: seemed to be reported as an efficacy outcome. Prevalent fractures were identified as a grade I deformity of the vertebral body by semi-quantitative assessment and following quantitative assessment, as < 20 % height decrease of the centre of the vertebral body compared with the anterior or posterior height of the vertebral body, or 25 % height decrease of the anterior vertebral body compared with the posterior vertebral body height. Incident vertebral fractures were defined as one grade progression of deformity of the vertebral body by semi-quantitative assessment and following quantitative assessment, as a 15 % progression of the vertebral body height and a 4 mm decrease in anterior, middle, or posterior vertebral body height.<br>Withdrawals due to adverse events: participant's safety was monitored and reported as adverse events. |
| Notes | Funding information: NR |
| ***Risk of bias*** | |

**Kasukawa 2014** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | 101 osteoporotic women were enrolled in this 1-year prospective study. Patients were randomly stratified into two groups—the R-group treated with risedronate alone at 17.5 mg/week, and the R + K-group treated with risedronate at 17.5 mg/week and menatetrenone at 45 mg/day. However, method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | High risk | No mention of blinding, or placebo control. Two arms involved different use of medications (risedronate+ menatetrenone versus risedronate alone) and likely open-labelled. The differences between two treatments would likely influence the participants' and personnel' performance. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | It was likely an open-labelled designed. However, the assessment of fractures appeared to require objective and clinical criteria, which would less likely influenced by the lack of blinding. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | It was likely an open-labelled designed, in which the assessment of subjective outcomes would probably be affected. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: "In both the R group and R + K group, the major reason for dropout was cessation of treatment by the patients themselves (n = 10 in each group). Nausea due to medication was the chief complaint in four patients in the R group and in seven patients in the R + K group"<br><br>Fractures appear to be reported as efficacy outcome. 1 year- Completion rate is 29/50 (58%) in 17.5 mg weekly group, and 26/51 (51%) in the combination group. Withdrawals due to adverse events are 8 in the 17.5 mg weekly group and 13 in the combination group, which was relatively balanced. Specific reasons for withdrawal were listed, and 10 participants in both groups did not specify a reason. Unclear how magnitude and direction of efficacy estimate will be affected. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Only one safety outcome, withdrawals due to adverse events, was reported and all randomised participants were accounted for. It was judged to be at low risk of bias. |
| Selective reporting (reporting bias) | Low risk | reported as planned in the method section |
| Other bias | Low risk | No other source of bias |

**Kato 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: 24 months<br><br>Blinding: double-blind |

**Kato 2010** *(Continued)*

| | |
|---|---|
| | Trial completion: NR/32<br>Risedronate + alfacalcidol: NR<br>Raloxifene + alfacalcidol: NR<br>Alfacalcidol: NR |
| Participants | Inclusion criteria: postmenopausal women.<br>Exclusion criteria: NR<br>Age: 71.6 (6.5) years<br>Time since menopause: NR<br>BMI: NR<br>Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: : NR<br>Previous bisphosphonate experience: NR<br>Source: Japan<br>Race: Asian, (100%) |
| Interventions | Three-arm comparison:<br>1. Risedronate + alfacalcidol: NR<br>2. Raloxifene + alfacalcidol: NR<br>3. Alfacalcidol: NR<br>(Background medication: NR.) |
| Outcomes | Radiographic vertebral fractures were only reported for L3 vertebra. The denominators of three groups were not known and it is not clear if there were other vertebral fractures.<br>None of the safety outcome of interest was reported. |
| Notes | 1. Funding information: NR.<br>2. This was a poster presentation abstract, from which no data were extractable. Details are described in Table 1, Appendix 5. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The study is a "randomised and double-blind trial..."<br>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 | Blinding approach was not provided and it was not clear whether the participants and personnel were well blinded. |

**Kato 2010** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | It was not clear whether the blinding was sufficient but the assessment for objective outcomes would less likely be biased. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | None of subjective outcomes of interest was addressed. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Participants were only assessed for fracture at their L3 vertebra. Zero incidents of vertebral fracture of L3 was reported but the number of randomised participants in each group was not provided. Data of this outcome was not usable. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | None of safety outcome data were extracted. |
| Selective reporting (reporting bias) | Unclear risk | None of outcome data is extracted and it is not clear if that is subject to other risk of bias given the reporting format of abstract. |
| Other bias | Unclear risk | The information contained in the abstract is less than sufficient to evaluate this domain. |

**Kendler 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | Multi-centre, randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: 24 months<br><br>Blinding: double-blind, double-dummy<br><br>Trial completion: 1013/1366 (74%)<br><br>Risedronate: 515/683 (75%)<br><br>Teriparatide: 498/683 (73%) |
| Participants | Inclusion criteria: ambulatory post-menopausal women older than 45 years of age with a bone mineral density T score ≤-1.5 SDs at the femoral neck, total hip, or lumbar spine. Participants had to have radiographic evidence of at least two moderate (i.e. a reduction in vertebral body height of 26% to 40%) or one severe (more than 40% reduction) prevalent vertebral fragility fracture according to the classification of Genant and colleagues.<br><br>Exclusion criteria: patients with unresolved skeletal diseases other than osteoporosis, malignant tumours in the 5 years before screening, osteonecrosis of the jaw, previous atypical subtrochanteric femoral fractures, risk factors for osteosarcoma, gastrointestinal disorders contraindicating risedronate, significantly impaired hepatic function, or a calculated creatinine clearance less than 30 mL/minute using the Cockcroft-Gault equation; patients who had undergone kyphoplasty or vertebroplasty at three or more levels before randomisation or within the 6 months before randomisation; Participants had to have normal baseline serum albumin-corrected calcium, parathyroid hormone, and free thyroxine concentrations, and 25-hydroxy-vitamin D concentration greater than 23 nmol/L. Previous treatment with osteoporosis medications was allowed if discontinued at the screening visit, with the following exceptions: (1) intravenous zoledronic acid if the last dose was administered less than 12 months before screening, (2) intravenous ibandronate or pamidronate if the last dose was administered less than 3 months before screening, (3) subcutaneous denosumab if the last dose was adminis- |

**Kendler 2018** *(Continued)*

| | |
|---|---|
| | tered less than 6 months before screening, (4) any treatment with parathyroid hormone, teriparatide, or other parathyroid hormone analogues, and (5) fluoride at therapeutic doses.<br><br>Age: 72.1 (8.7) years<br><br>Time since menopause: NR<br><br>BMI: 27.0 (4.6) kg/$m^2$<br><br>Lumbar spine BMD: 0.86 (0.15) g/$cm^2$, femoral neck BMD: 0.67 (0.11) g/$cm^2$<br><br>Lumbar spine T-score: -2.28 (1.23), femoral neck T-score: -2.23 (0.75)<br><br>Prevalent vertebral fractures: 1358/1360 (100%)<br><br>Previous bisphosphonate experience: 788/1360 (58%)<br><br>Source: Argentina, Austria, Belgium, Brazil, Canada, Czechia, France, Germany, Greece, Hungary, Italy, Poland, Puerto Rico, Spain,USA<br><br>Race: Caucasian (97%); Asian (1%); Black/African-American (1%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 35 mg once weekly + placebo ( of teriparatide), SC daily<br><br>2. Teriparatide 20 µg/day, SC + placebo (of risedronate) once weekly<br><br>(All participants received daily calcium 500 mg to 1000 mg and roughly 400 IU to 800 IU of vitamin D3 or D2; In patients with 25-hydroxy-vitamin D concentrations of 23 to 50 nmol/L at screening, the supplemental dose of vitamin D was 2000 IU per day.) |
| Outcomes | Radiographic vertebral fractures: were assessed as a primary efficacy endpoint. Lateral spine radiographs were repeated at 12 and 24 months or early termination for new vertebral fractures. Additional unscheduled radiographs were done at any interim visit to detect new clinical vertebral fractures if the patient reported back pain clinically suggestive of a vertebral fracture. A central radiologist (at BioClinica, San Francisco, CA, USA) assessed the incidents of new vertebral fractures by quantitative vertebral morphometry, confirmed with qualitative visual semi-quantitative grading, according to the scale by Genant and colleagues. A new vertebral fracture was defined as a vertebral body height loss of at least 20% (and 4 mm) of a vertebra that was un-fractured at baseline, based on a 6-point placement of the vertebral bodies from T4 to L4, and confirmed by an increase by one or more severity grades.<br><br>Non-vertebral and clinical vertebral fracture: were assessed as secondary efficacy endpoint. A non-vertebral fracture is a fracture at any of the following non-vertebral sites: clavicle, scapula, ribs, sternum, sacrum, coccyx, humerus, radius, ulna, carpus, pelvis, hip, femur, patella, tibia, fibula, ankle, calcaneus, tarsus, and metatarsal. Non-vertebral fractures will be determined by direct questioning at each visit, and will be confirmed by the site investigators by x-ray, radiology or surgical report. A clinical vertebral fracture is defined as a new or worsening vertebral fracture, confirmed by radiography, that was associated with signs and symptoms highly suggestive of a vertebral fracture.<br><br>Health-related quality of life: assessed using the EQ-5D-5L questionnaire, which comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).<br><br>Withdrawals due to adverse events, serious adverse events, atypical femoral fractures, atrial fibrillation and osteonecrosis of the jaw: Participant's safety was monitored through the study and events were reported as adverse events. |
| Notes | 1. Funded by Lilly.<br><br>2. VERO study: The VERtebral fracture treatment comparisons in Osteoporotic women. Trial registry number: NCT01709110. |

***Risk of bias***

**Kendler 2018** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote:"We randomly assigned patients (1:1) to receive either injectable subcutaneous teriparatide (20 µg daily; Forteo®, Lilly) plus an oral weekly placebo, or oral risedronate (35 mg weekly; Actonel®, Warner-Chilcott) plus injectable subcutaneous daily placebo. Randomisation was stratified by history of clinical vertebral fragility fracture (<12 months vs >12 months before screening), and by recent use of bisphosphonates...Assignment to treatment groups was determined by an interactive voice-response system, based on a computer-generated random sequence prepared by Lilly." |
| Allocation concealment (selection bias) | Low risk | In addition to above,quote:"Patients, investigators, central imaging radiologists, and sponsor representatives were blinded to treatment assignment." |
| Blinding of participants and personnel (performance bias) | Low risk | Quote:"We randomly assigned patients (1:1) to receive either injectable subcutaneous teriparatide (20 µg daily; Forteo®, Lilly) plus an oral weekly placebo, or oral risedronate (35 mg weekly; Actonel®, Warner-Chilcott) plus injectable subcutaneous daily placebo. Placebos were matched for colour, shape, and size."<br><br>Blinding approaches were appropriate. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding approaches were appropriate and the assessment of the objective outcomes was less likely biased. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding approaches were appropriate and would prevent the assessment of subjective outcomes being biased. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote:"We analysed efficacy following a modified intention-to-treat principle and included randomly assigned patients who received at least one dose of investigational product (full analysis set). For analysis of the primary outcome, we included only patients with at least one evaluable spinal radiograph at baseline and at least one after baseline (modified full analysis set). Sensitivity analyses were done for the per-protocol population, which included all patients without major protocol deviations as predefined in the analysis plan. No imputation was made for fracture data. Patients with missing x-ray data at 24 months and no evidence of vertebral fracture during the 24-month study period did not contribute to the analyses."<br><br>The overall complete rate 75% (1031/1366) and the withdrawal numbers and reasons seemed balanced between two treatment groups; sensitivity analyses were conducted. However, the approach to handling the missing data were not provided and the attrition bias might impact the estimate of effect size. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | Statistical methods were not provided for safety outcomes. The approach to handling the missing data were not provided, either. In addition to the less-than-80% completion rates, it was judged to be at high risk of bias. |
| Selective reporting (reporting bias) | Low risk | All of the outcomes appeared to be reported as planned in both the publication and registered protocol (NCT01709110). |
| Other bias | Low risk | It appeared to have no other sources of bias. |

**Leung 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Multi-centre, randomised and placebo-controlled trial<br>Secondary prevention<br>Duration: one year<br>Blinding: double-blind<br>Trial completion: 60/65 (92%)<br>Risedronate: NR/31<br>Placebo: NR/34 |
| Participants | Inclusion criteria: women postmenopausal for 5 or more years with spine BMD at L1- 4 < 2.5 SD of the local peak young mean value.<br>Exclusion criteria: had used oestrogen or oestrogen-related drugs in the preceding 12 months, bisphosphonates or fluoride in preceding 6 months, vitamin D supplementation in preceding 3 months, calcitonin or calcitriol in preceding 1 month, history of metabolic bone disease, impaired renal and liver function, history of recent major gastrointestinal disease or other major medical disease; vertebral Xray demonstrating physical abnormalities of the spine which would affect the lumbar BMD such as aortic calcifications, severe osteoarthritis, scoliosis, 2 or more lumbar spine fractures or 5 or more vertebral fractures.<br>Age: 67 (0.6) years<br>Time since menopause: 15.3 (1.9) years<br>BMI: 32.7 kg/m$^2$<br>Lumbar spine BMD: 0.61 (0.06) g/cm$^2$, femoral neck BMD: 0.51 (0.07) g/cm$^2$<br>Lumbar spine T-score: -3.2 (0.5), femoral neck T-score: -2.6 (0.7)<br>Prevalent vertebral fractures: 18/65 (28%)<br>Previous bisphosphonate experience: NR<br>Source: China<br>Race: Asian (100%) |
| Interventions | Two-arm comparison:<br>1. Risedronate 5 mg/day<br>2. Placebo<br>(All participants received daily calcium 500 mg and vitamin D 400 IU.) |
| Outcomes | Non-vertebral, hip, wrist, and clinical vertebral fractures, serious adverse events and gastrointestinal adverse events: ascertainment was not specified and monitored as safety outcome. |
| Notes | Funded by Aventis Pharma, Ltd. |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |

**Leung 2005** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote:"This was a multi-centre, randomised, double-blind, placebo-controlled study. The patients were randomised to receive either risedronate (Actonel, Aventis Pharma) 5 mg daily or matching placebo."<br><br>Method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote:"The patients were randomised to receive either risedronate (Actonel, Aventis Pharma) 5 mg daily or matching placebo."<br><br>Blinding approach was appropriate for participants and personnel. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding approach was appropriate. In addition, the assessment of fracture outcomes was based on objective and clinical evidence, which was less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding approach was appropriate to avoid the bias in the assessment for subjective outcomes. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Fracture outcomes were reported as adverse events. One-year completion rate was 60/65 (92%) but not separated by treatment group. WDAE were balanced across groups. It was judged to be at low risk of bias. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | As above, the overall completion rate was good. The small amount of missing data would not bias the results. |
| Selective reporting (reporting bias) | Low risk | Protocol was not available. However, the outcomes were reported as planned in the method section. |
| Other bias | Low risk | No other source of bias was observed. |

**Li 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and placebo-controlled trial<br><br>Secondary prevention<br><br>Duration: 12 months<br><br>Blinding: double-blind<br><br>Trial completion: 54/60 (90%)<br><br>Risedronate: 28/30 (93%)<br><br>Placebo: 26/30 (87%) |
| Participants | Inclusion criteria: women who were between 45 and 68 years old, at least 1 year past menopause, in generally good health without organ disease or hobby of smoke or alcohol, and had at least 3 evaluable lumbar vertebral bodies without fracture or degenerative disease, and whose T-scores of lumber spine BMD was ≤ -2.5. |

**Li 2005** *(Continued)*

| | |
|---|---|
| | Exclusion criteria: any other bone metabolic diseases or receiving drugs that affected the bone metabolism.<br>Age: NR<br>Time since menopause: NR<br>BMI: NR<br>Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: NR<br>Source: China<br>Race: Asian (100%) |
| Interventions | Two-arm comparison:<br>1. Risedronate 5 mg/day<br>2. Placebo<br>(All participants received daily calcium 600 mg and vitamin D 125 IU.) |
| Outcomes | Non-vertebral, hip, wrist, clinical vertebral and atypical femoral fractures: ascertainment was not specified and monitored as safety outcome. All fracture outcomes were inferred "0" from the text .<br>Withdrawals due to adverse events: monitored as adverse events. |
| Notes | Funding Information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote:"...divided into two groups randomly, risedronate treatment group and placebo control group."<br>Method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote:"The placebo was the same as risedronate in appearance."<br>Identical placebo was used to maintain the blinding of participants and personnel. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Blinding method was appropriate. In addition, the assessment of fracture outcomes was based on objective and clinical evidence, which was less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding approach was appropriate to avoid the bias in the assessment for subjective outcomes. |

**Li 2005** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Fractures reported as adverse events. One-year completion rate overall was 26/30 (87%) in placebo group and 28/30 (93%) in risedronate group. Reasons for withdrawal were reasonably balanced. Analysis population was unclear. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | As above, the attrition bias was trivial and less likely bias the results. |
| Selective reporting (reporting bias) | Low risk | No protocol was found. However, all of the outcomes were reported as described in methods/abstract. |
| Other bias | Low risk | No other source of bias was observed. |

**Lim 2017**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised trial<br>Not clear if primary or secondary prevention<br>Duration: unclear<br>Blinding: open-label<br>Trial completion: NR/281<br>Risedronate: NR/141<br>HRT: NR/140 |
| Participants | Inclusion criteria: women 50 or older with acute, first-time, and lower-energy trauma hip fracture.<br>Exclusion criteria: NR<br>Age: NR<br>Time since menopause: NR<br>BMI: NR<br>Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: NR<br>Source: NR<br>Race: NR |
| Interventions | Two-arm comparison:<br>1. Risedronate 35 mg once weekly<br>2. HRT: 17beta-estradiol gel 1.5 g/day<br>(Background information: NR.) |

**Lim 2017** *(Continued)*

| | |
|---|---|
| Outcomes | New clinical fractures were reported but not by anatomic location. Data were not extractable but described in Table 1, Appendix 5.<br><br>None of the safety outcomes of interest were reported. |
| Notes | 1. Funding information: NR.<br><br>2. A conference abstract. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote:"...a prospective, open label, randomised trial..."<br>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 | It was an open-label study in which two compared treatments had different dose schedules (daily versus weekly). The participants' and personnel's performance were likely influenced by their knowledge of their assigned medication. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | Fracture outcomes were reported, but not by anatomic locations. None of the objective outcome data were usable. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | None of subjective outcomes of interest were reported. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | As above, none of efficacy outcome data were extracted for analysis. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | As above, none of safety outcome data were extracted for analysis. |
| Selective reporting (reporting bias) | Unclear risk | It was judged to be at unclear risk of bias given that the information provided in the abstract was insufficient to reach a conclusion. |
| Other bias | Unclear risk | All the information was extract from the abstract. It was not clear if any important bias would have been introduced. |

**McClung 2001**

***Study characteristics***

| | |
|---|---|
| Methods | Randomised, placebo-controlled trial<br><br>Secondary prevention<br><br>Duration: three years<br><br>Blinding: double-blind |

**McClung 2001** *(Continued)*

| | |
|---|---|
| | Trial completion: 6007/9331 (64%)<br><br>Risedronate: 4000/6197 (65%)<br><br>Placebo: 2007/3134 (64%) |
| Participants | Inclusion criteria: Group 1 - Women age 70 to 79 years with osteoporosis defined as femoral neck BMD T-score > 4 SD below peak bone mass (originally calculated according to densitometer reference data base and later according to Third National Health and Nutrition Examination Survey) or > -3 SD and at least one clinical risk factor i.e. difficulty standing from a sitting position, poor tandem gait, fall-related injury in previous year, psychomotor score = 5 on Clifton Modified Gibson Spiral Maze test, smoking during previous 5 years, maternal history of hip fracture, previous hip fracture, hip axis length = 11.1cm. Group 2 - Women age 80 or older with at least one non-skeletal risk factor for hip fracture, a femoral-neck T score < -4 or a femoral-neck T score < -3 plus a hip axis length = 11.1cm or greater.<br><br>Exclusion criteria: any major medical illness, a recent history of cancer, another metabolic bone disease within the previous year, important abnormalities in the results of routine laboratory tests, recent use of drugs known to affect bone, allergy to any bisphosphonate, a history of bilateral hip fractures, and any physical or mental condition that would preclude participation in a clinical trial. There were no specific criteria for exclusion on the basis of previous or ongoing upper gastrointestinal tract disorders or concomitant use of non-steroidal anti-inflammatory drugs, aspirin, proton-pump inhibitors, or antacids.<br><br>Age: 77.8 (5.4) years<br><br>Time since menopause: 31.7 (8.8) years<br><br>BMI: 25.0 kg/m$^2$<br><br>Lumbar spine BMD:NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: NR, femoral neck T-score: -3.7 (0.6), for Group 1<br><br>Prevalent vertebral fractures: 2799/9331 (30%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: 183 study centres in North America, Europe, New Zealand, and Australia<br><br>Race: Caucasian (98%) |
| Interventions | Two-arm comparison for both Group 1 (age 70 to 79) and 2 (age 80+):<br><br>1. Risedronate 2.5 mg/day or 5 mg/day<br><br>2. Placebo<br><br>(All participants received daily calcium 1000 mg. Patients would received vitamin D 500 IU/day if their 25-hydroxyvitamin level was < 40 nmol/L at the time of screening.) |
| Outcomes | Hip Fractures: assessed as primary efficacy end point and confirmed by radiographic evidence.<br><br>Non-vertebral fractures: assessed as secondary efficacy end point and fractures of wrist, leg, humerus, hip, pelvis, or clavicle were confirmed by radiographic evidence.<br><br>Withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events: Participant's safety was monitored through the study and events were reported as adverse events. The outcome of withdrawals due to adverse events was reported as the numbers of participants withdrawn from the treatment (instead of from the study) due to adverse events. |
| Notes | 1. Funded by grants from Procter & Gamble Pharmaceuticals (Cincinnati) and Aventis Pharma (Bridgewater, N.J.)<br><br>2. Hip Intervention Program Study. |

**McClung 2001** *(Continued)*

3. For data analysis, "Risedronate 2.5 or 5 mg/day" would be extracted as "Risedronate 5 mg/day" in the base case. A sensitivity analysis of excluding it would be conducted to test the robustness of the result.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The women in each of the two enrolment groups were randomly assigned."<br><br>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) | Low risk | Quote: "The women in each of the two enrolment groups were randomly assigned to take either a 2.5-mg or a 5.0-mg risedronate tablet or an identical-appearing placebo tablet." and "The HIP study3 was a 3-year, double-blind, placebo controlled, randomized study (Masud 2009).. "<br><br>A double-blind study and matched placebos were used. The blinding was appropriate to prevent performance bias. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "The primary end point was the incidence of radiographically confirmed hip fractures. A secondary end point was the incidence of non vertebral osteoporotic fractures, defined as all radiographically confirmed fractures of the wrist, leg, humerus, hip, pelvis, or clavicle."<br><br>Matched placebos were used to maintain the blindness. In addition to the above blinding approach, the assessment of the objective outcomes were less likely biased. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | A double-blind study and matched placebos were used. The blinding was sufficient to prevent detection bias. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: "Women who received at least one dose of either risedronate or placebo were included in the analysis. Women who discontinued treatment before the end of the three-year treatment period were requested to return to their study centre at the time of the scheduled third-year visit. We performed analyses of fractures that occurred during the treatment period as well as those that occurred during treatment or follow-up."<br><br>As reported, all the randomised participants included in the analysis, except for 166 (2%) not taking the medicine. In Figure 1: 64% (2007/3114) of the placebo group and 65% (4000/6197) of the risedronate group completed the 3-year study, respectively. Although the study was trying to follow up the participants early discontinuing the treatment, the completion rates, defined as who completed follow-up, of 2 groups were less than 80%. It was judged to be at high risk of bias given that portion of missing data might bias the effect estimates of interest. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | As above, and the statistical analysis for safety outcomes of interest was not provided. It was judged to be at high risk of bias given that the completion rates of 2 groups were less than 80%. Without an appropriate approach to handling the missing data, the effect estimates of interest would likely to be biased. |

**McClung 2001** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | Protocol was not available but the outcomes of interest were reported as described in the method section. However, it reads quote: "We planned to compare the women who were assigned to risedronate at each dose with those assigned to placebo. However, because the incidents of hip fractures was lower than expected and because another study of risedronate showed that both a 2.5-mg dose and a 5.0-mg dose were effective in reducing the risk of vertebral fractures, we modified the analysis of efficacy and compared the women assigned to risedronate at either dose with those assigned to placebo."<br><br>Some of the reported results combined 2.5-mg and a 5.0-mg dose of risedronate, which did not seem pre-planned and would likely bias the effect estimates of the outcomes of interest. |
| Other bias | Low risk | None was detected. |

**McClung 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | Multi-centre, randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: two years<br><br>Blinding: double-blind<br><br>Trial completion: 722/922 (78%)<br><br>Risedronate 5 mg/day: 248/307 (81%)<br><br>Risedronate 35 mg/week, at least 30 min before breakfast: 234/308 (76%)<br><br>Risedronate 35 mg/week, immediately following breakfast: 240/307 (78%) |
| Participants | Inclusion criteria: at least 50 years of age, ambulatory, in generally good health, postmenopausal (at least 5 years since last menses), had at least three vertebral bodies in the lumbar spine (L1 to L4) evaluable by densitometry (i.e. without fracture or degenerative disease), and had a lumbar spine or total hip BMD corresponding to a T-score of -2.5 or lower or a T-score of -2.0 or lower with at least one prevalent vertebral fracture (T4 to L4).<br><br>Exclusion criteria: contraindications to oral bisphosphonate therapy, lumbar spine BMD corresponding to a T-score of ≤-5, use of medications that could interfere with the study evaluations, conditions that would interfere with the BMD measurements, bilateral hip prostheses, BMI > 32 kg/m$^2$, allergy to bisphosphonates, history of cancer in the last 5 years (excluding basal or squamous skin cancers or successfully treated cervical cancer in situ), drug or alcohol abuse, abnormal clinical laboratory measurements, creatinine clearance < 30 mL/minute, hypo- or hypercalcaemia, history of hyperparathyroidism or hyperthyroidism (unless corrected), osteomalacia, and any previous or ongoing condition that the investigator judged could prevent the subject from being able to complete the study.<br><br>Age: 65.7 (4.3) years<br><br>Time since menopause: 18.2 (4.9) years<br><br>BMI: NR<br><br>Lumbar spine BMD: 0.76 (0.04) g/cm$^2$, femoral neck BMD: 0.59 (0.10)<br><br>Lumbar spine T-score: -3.11 (0.36), femoral neck T-score: -2.95 (0.82) |

**McClung 2012** *(Continued)*

| | |
|---|---|
| | Prevalent vertebral fractures: 238/922 (26%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: 43 study centres in North America, South America, and the European Union<br><br>Race: NR or white (99%), Asian (0.2%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate immediate-release (IR) 5 mg/day<br><br>2. Risedronate delayed-release (DR) 35 mg once weekly, at least 30 min before breakfast<br><br>3. Risedronate DR 35 mg once weekly, immediately following breakfast<br><br>(All participants received daily calcium 1000 mg and vitamin D 800 IU to 1000 IU.) |
| Outcomes | Radiographic vertebral fractures: an efficacy outcome and were assessed by semi-quantitative morphometric analysis of lateral thoracic and lumbar spine radiographs collected at screening and after 52 and 104 weeks. Radiographs were reviewed for quality and analysed for fracture at a central site.<br><br>Non-vertebral and clinical vertebral fractures, withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, osteonecrosis of the jaw, atrial fibrillation, and acute phase reaction: ascertainment was not specified. Incidents were reported as adverse events. |
| Notes | 1. Funded by Warner Chilcott Pharmaceuticals Inc. (formerly Procter & Gamble Pharmaceuticals, Inc.) and Sanofi Aventis, Inc. for the design and conduct of the study.<br><br>2. Trial Registry Number: NCT00541658.<br><br>3. All of the three arms have the same weekly dose. This study was not included in the quantitative synthesis. Details are in Table 2, Appendix 5. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Eligible subjects who gave consent were stratified by anticoagulant use (since fecal occult blood testing was performed during the study) and randomly assigned in a 1:1:1 ratio to the three treatment groups."<br><br>Method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "Subjects received oral risedronate 5 mg IR daily at least 30 min before breakfast or risedronate 35 mg DR once a week, taken either at least 30 min before or immediately following breakfast. All subjects took nine study tablets each week: an IR study tablet daily plus a DR study tablet before breakfast and another following breakfast on a single specified day of the week. All placebo tablets were identical in appearance to their corresponding 5 mg IR and 35 mg DR active tablets and supplied in identical blister cards."<br><br>Blinding approaches were judged sufficient to prevent participants' and personnel's performance bias. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "...Radiographs were reviewed for quality and analysed for fracture at a central site (Synarc, San Francisco, CA, USA). "<br><br>Blinding approaches were appropriate. |

**McClung 2012** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Matched placebos were used and relevant approaches were appropriate to prevent detection bias for subjective outcomes. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Vertebral morphometric fractures were efficacy outcomes, and vertebral and clinical vertebral fractures were reported as adverse events. Completion rate was 247/307 (80%) in 5 mg daily group, 240/308 (78%) in the weekly 35 mg group (before breakfast), and 73/307 (76%) in the weekly 35 mg group (following breakfast). WDAE ranged from 8.1% to 12.0% in Risedronate 35 mg/week groups. Other reasons for early discontinuation were balanced across groups. Although, the approach to handling missing data were not provided, the bias would be minor. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | As above, given the fine completion rates and balanced early discontinuation across groups, it was judged to be at low risk of bias. |
| Selective reporting (reporting bias) | Low risk | Protocol was not found. However, the published text appeared to report same outcomes in the registered protocol (NCT00541658). |
| Other bias | Low risk | None was detected. |

**Mortensen 1998**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Randomised and placebo-controlled trial<br><br>Primary prevention<br><br>Duration: two years on drug plus the third year drug free follow-up. (Patients given option to continue in study after completing the first year.)<br><br>Blinding: double-blind<br><br>Trial completion: 96/111 (86%)<br><br>Risedronate 5 mg/day: 32/37 (86%)<br><br>Risedronate 5 mg/day, cyclic: 32/38 (84%)<br><br>Placebo: 32/36 (89%) |
| Participants | Inclusion criteria: ambulatory, active women 6 to 60 months postmenopausal (as measured by FSH and estradiol) weighing 45 kg to 90 kg (within 25% of normal height and weight). Lumbar spine within 2 SD of age-matched bone mass.<br><br>Exclusion criteria: receiving bisphosphonates, thyroid hormone therapy, glucocorticoids = 5 mg/day, anabolic agents, calcitonin, vitamin D > 400 IU/day, calcium > 1500/day, diuretics, anticonvulsants > 1 month in previous 6 months, HRT > 1 month in previous 6 months, fluoride > 1 month ever; any bone disease including hyperparathyroidism; alcohol or drug abuse; psychiatric disease; any evidence of osteoporosis - vertebral deformity or osteoporosis related fracture of hip or wrist, bilateral oophorectomy, or artificial menopause.<br><br>Age: 51.5 (3.8) years<br><br>Time since menopause: 2.7 (1.7) years<br><br>BMI: NR |

**Mortensen 1998** *(Continued)*

| | |
|---|---|
| | Lumbar spine BMD: 0.94 (1.15) g/cm$^2$, femoral neck BMD: 0.73 (0.10) g/cm$^2$<br><br>Lumbar spine T-score: NR; femoral neck T-score: NR<br><br>Prevalent vertebral fractures: 0%<br><br>Previous bisphosphonate experience: NR<br><br>Source: Denmark and USA<br><br>Race: Caucasian (100%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Risedronate 5 mg/day, cyclic: risedronate 5 mg/day for first 2 weeks of every calendar month followed by oral placebo for remainder<br><br>3. Placebo<br><br>(Participants were not required to take supplemental calcium.) |
| Outcomes | Radiographic vertebral fractures - Radiographs of the thoracic and lumbar spine were taken before the study, at months 7, 13, and 25, and at 12 months after cessation of treatment, for the appearance of vertebral deformities for safety purposes. Vertebral deformities were defined as 25% or more decrease in anterior, mid, and/or posterior height of a vertebral body compared to baseline.<br><br>None of the safety outcomes of interest were reported. |
| Notes | 1. Funded by Procter & Gamble Pharmaceuticals.<br><br>2. Only the 1-year data is eligible so extracted. The arm of "Risedronate 5 mg/day, cyclic" is not an approved use so data not included in the quantitative synthesis. Details are in Table 3, Appendix 5. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were stratified based on calcium intake and then randomly assigned to receive …"<br>The method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, the method for sequence generation was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: “This double-blind, placebo-controlled study was conducted at two study centres…The placebo capsules were identical in appearance to the risedronate capsules. All test materials were prepared by Procter & Gamble Pharmaceuticals…..The blind-regarding-treatment assignment was maintained throughout the study."<br><br>Blinding approaches were appropriate and the blinding throughout the study was confirmed. The performance bias was effectively avoided. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "Radiographs of the thoracic and lumbar spine were taken before the study, at months 7, 13, and 25, and at 12 months after cessation of treatment. They were evaluated for the appearance of vertebral deformities for safety purposes. Vertebral deformities were defined as 25% or more decrease in anterior, mid, and/or posterior height of a vertebral body compared to baseline.”<br><br>Blinding approaches were sufficient for the objective outcomes assessment. |

**Mortensen 1998** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Blinding approaches were sufficient for the subjective outcomes assessment. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Quote: “After 1 yr of participation in the study, patients were offered three options: 1) to discontinue from the study, 2) to complete a second year without therapy, or 3) to continue the blinded study for an additional year and to complete 1 yr without treatment thereafter. The population of primary interest for effectiveness and safety was the “intent-to-treat” population, which included all available data from patients randomised into the study.” This was a 3-year study, with 2-year on treatment and 1-year follow-up off treatment. Only the 1-year data when patients used the assigned treatment was extracted. 89% (32/36), 84% (32/38) and 86% (32/37) completed the first year study (the reasons of early discontinuation were not reported)."<br><br>It was judged to be at low risk of bias, given that the completion rates were greater than 80% across the groups. The small portion of missing data would unlikely significantly bias the efficacy estimates. Fracture outcomes were reported as adverse events. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | As above, it was judged to be low risk of bias, given the high completion rates across the groups. |
| 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 appeared to be free of other risks of bias. |

**Muscoso 2004**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: two years<br><br>Blinding: NR<br><br>Trial completion: NR/2000<br><br>Risedronate: NR/100<br><br>Alendronate: NR/1000<br><br>Clodronate: NR/800<br><br>Raloxifene: NR/100 |
| Participants | Inclusion criteria: a total of 2000 female patients with osteoporosis were enrolled in the study.<br><br>Exclusion criteria: NR<br><br>Age: 68 (9) years<br><br>Time since menopause: NR<br><br>BMI: NR |

**Muscoso 2004** *(Continued)*

| | |
|---|---|
| | Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: NR; femoral neck T-score: NR<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: NR<br>Source: Italy<br>Race: NR |
| Interventions | Four-arm comparison:<br>1. Risedronate 5 mg/day<br>2. Alendronate 10 mg/day<br>3. Clodronate 100 mg/week, IM<br>4. Raloxifene 60 mg/day<br>(All participants received daily calcium 1000 mg and vitamin D 800IU.) |
| Outcomes | Events of non-vertebral, wrist, hip and clinical vertebral fractures were reported. It was not clear if those were reported as adverse events.<br>None of the safety outcomes of interest were reported. |
| Notes | Funding information: NR. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The patients were divided at random into the following 4 groups..."<br>Method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | High risk | Blinding was not mentioned, but it was very likely to be an open-label head-to-head comparison trial given the different drug administration routes (oral versus intramuscular) and dose schedule (daily versus weekly). The participants and personnel were likely un-blinded and influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Although it was very likely to be an open-label head-to-head comparison trial, the assessment for fractures (objective outcomes) were based on clinical evidence and professional judgment, which was less likely to be biased by the lack of or ineffective blinding. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | None of the safety outcomes of interest were reported. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Radiographic vertebral, non-vertebral, wrist, hip and clinical fractures were reported. No information about statistical strategy and attrition was reported. |
| Incomplete outcome data (attrition bias) | Unclear risk | None of the safety outcome data were extracted. |

**Muscoso 2004** *(Continued)*

Safety Outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | No safety outcome was reported, which barely met the reporting practice of clinical trials. |
| Other bias | Unclear risk | The descriptions of the study and results were less than sufficient for assessment. It was not clear if any important bias would have been introduced. |

**Nakamura 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | Multi-centre, randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: three years<br><br>Blinding: double-blind<br><br>Trial completion: 854/1141*<br><br>Risedronate: NR/371*<br><br>Ibandronate 0.5 mg/month: NR/389*<br><br>Ibandronate 1 mg/month: NR/381*<br><br>(*A total of 1141 female patients were randomised and received study medication. Gender information about the 37 patients who were randomised but not receive study treatment and the completers were not provided.) |
| Participants | Inclusion criteria: ambulatory women or men aged ≧ 60 years with primary osteoporosis according to the Diagnosis Criteria of Primary Osteoporosis in Japan were eligible if they had: fragile bone fracture (nontraumatic osteoporotic fracture that occurred by slight external force combined with low BMD); BMD of the lumbar spine (L2-L4), or proximal femur (total hip and femoral neck) < 80 % of the young adult mean (equivalent to T score -1.7, -1.6, and -1.4, respectively); and 1-5 radiographically confirmed vertebral fractures in the fourth thoracic spine-fourth lumbar spine (Th4-L4)<br><br>Exclusion criteria: Vertebral deformations likely to affect vertebral strength; previous radiotherapy of the thoracic spine/lumbar spine/pelvis; secondary osteoporosis or a disease causing decrease in bone volume; a disorder delaying the passage of food through the oesophagus; received/planned invasive dental procedures; bisphosphonate use within 1 year of the start of the study, or prior treatment with ibandronate, anti-RANKL antibody (AMG162) or strontium; receipt of drugs likely to affect bone metabolism within 8 weeks of the start of the study; severe cardiac, renal or hepatic disease; calcium outside the criteria value (i.e. < 8.4 mg/dL or > 10.4 mg/dL); hypersensitivity to bisphosphonate, calcium or vitamin D; active malignant tumour or prior therapy for malignant tumour within 3 years.<br><br>Age: 72.7 (6.3) years<br><br>Time since menopause: NR<br><br>BMI: 22.8 kg/m$^2$<br><br>Lumbar spine BMD: g/cm$^2$, femoral neck BMD: NR<br><br>Lumbar spine T-score: -2.66 (1.03), femoral neck T-score: -2.47 (0.77)<br><br>Prevalent vertebral fractures: 1141/1141 (100%)<br><br>Previous bisphosphonate experience: NR |

**Nakamura 2013** *(Continued)*

| | |
|---|---|
| | Source: Japan<br><br>Race: Asian (100%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 2.5 mg/day + placebo (of ibandronate), IV<br><br>2. Ibandronate 0.5 mg/month, IV + placebo (of risedronate)<br><br>3) Ibandronate 1 mg/month, IV + placebo (of risedronate)<br><br>(All participants received daily calcium 305 mg and vitamin D 200 IU.) |
| Outcomes | Radiographic vertebral fractures: was assessed as primary efficacy end point. Radiographs of the thoracic and lumbar spine were taken at screening, baseline, and at 6, 12, 24, and 36 months after treatment for the assessment of fractures. To identify morphometric vertebral fractures, the vertebral bodies of the lateral projection from Th4 to L4 were assessed using semi-quantitative (SQ) methodology and quantitative morphometry (QM) by a central committee who were blinded to treatment. A new vertebral fracture was defined as an increase of ≥ 1 SQ grading scale in a vertebra that was normal at baseline, while a worsening fracture was defined as an increase of ≥ 1 SQ grading scale in a vertebra that was deformed at baseline. Fracture incidents were adjudicated by three experts with reference to QM data from Synarc (San Francisco) and a binary SQ assessment was made.<br><br>Osteonecrosis of the jaw and atypical femoral neck: Participant's safety was monitored and incidents were reported as adverse events. |
| Notes | 1. Funded by Chugai Pharmaceutical Co. Ltd. and Taisho Pharmaceutical Co. Ltd.<br><br>2. MOVER (MOnthly intraVenous ibandronatE versus daily oral Risedronate) study, trial registry number: NCT004479154.<br><br>3. This study included male participants but reported fracture data specifically for osteoporotic women; and the incident of osteonecrosis of the jaw and atypical femoral neck were inferred "0". However, the baseline characteristics included 8.8%, 5.3% and 7.3% male participants in Risedronate, Ibandronate 0.5 mg/month and Ibandronate 1 mg/moth group, respectively. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed centrally through dynamic allocation (minimization method) based on the number of prevalent vertebral fractures (1 vs. >1)."<br><br>Method was described and appropriate. |
| Allocation concealment (selection bias) | Low risk | Quote: Quote: "Randomization was performed centrally; Patients, investigators, steering committee members, the sponsor, and the faculty who adjudicated the study end points remained unaware of treatment-group assignments throughout the trial." |
| Blinding of participants and personnel (performance bias) | Unclear risk | Quote: "double-blind, active drug-controlled"; "Patients were randomly assigned to receive: 0.5 mg/month IV ibandronate (F. Hoffmann-La Roche, Ltd.) plus oral daily placebo for 36 months; 1 mg/month IV ibandronate plus oral daily placebo; or 2.5 mg/day oral risedronate (Ajinomoto Co. Inc.) plus IV placebo by the double dummy method..."<br><br>Double-dummy method was used but the respective placebos were not described. It was not clear how identical they were and if there were other method to maintain the blindness of participants and personnel. |

**Nakamura 2013** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "To identify morphometric vertebral fractures, the vertebral bodies of the lateral projection from Th4 to L4 were assessed using semi-quantitative (SQ) methodology and quantitative morphometry (QM) by a central committee who were blinded to treatment."<br><br>Although the effectiveness of the blinding method was in question, the assessment of fractures was based on clinical and objective evidence which were less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | As above, it was not clear if the placebo was identical (matched) to the active drug and if the assessor for the safety outcomes were maintained blinded. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: "The primary analysis was performed on the per-protocol set (PPS)...Missing data were imputed by the last observation carried forward method...Overall, 909 patients (854 women) completed the study....No difference in discontinuation rate was found between the groups: 25.8, 24.6 and 27.6 %, respectively."<br><br>Radiographic vertebral fractures were evaluated as primary endpoint. The randomised numbers for each group were not provided. Given the safety population for women (371+389+381=1141), the overall completion rate was inferred to be less than 75%, (854/1141). Some of the withdrawal reasons (e.g. "patient choose to withdraw" and "other") did not seem balanced across the groups. It was judged to be at high risk of bias. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | Only osteonecrosis of the jaw and atypical femoral neck were extracted as safety outcomes, both of which were inferred "0" from no such event in the whole population. In addition to the overall completion rate(<75%) and the imbalanced discontinuations across groups, death numbers were not consistently reported in Figure 1 (1 in ibandronate 0.5 mg/m, 0 in ibandronate 1 mg/m and 2 in risedronate 5 mg/day group) and Table 2 (AE leading to death: 5 in ibandronate 0.5 mg/m, 3 in ibandronate 1 mg/m and 6 in risedronate 5 mg/day group). it was judged to be at high risk of bias. |
| Selective reporting (reporting bias) | Low risk | The reported outcomes were the same as described in the registered protocol (NCT004479154). |
| Other bias | Low risk | None was detected. |

**Narula 2012**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: one year<br><br>Blinding: NR<br><br>Trial completion: 42/190 (22%)<br><br>Risedronate: 24/148 (16%)<br><br>Strontium ranelate: 18/42 (43%) |

**Narula 2012** *(Continued)*

| | |
|---|---|
| Participants | Inclusion criteria: women between 40 to 80 years, who were post-menopausal for at least one year and had osteopenia or osteoporosis and in whom BMD was not possible but they had fragility fractures and radiographs showed gross decrease in bone density, in good health with no vertebral abnormalities in the L1-L4 region which interferes with measurement of BMD by DEXA and had decreased BMD (lumbar spine or right or left femoral neck or both, T-score -1.0 or less).<br><br>Exclusion criteria: deranged renal function (serum creatinine > 1.5 mg %) or renal calculi, abnormal thyroid function (serum TSH between 0.5 to 5.0 mIU/L), significant liver disease requiring prescription medication within the previous five years, regular therapy with a phosphate binding antacid, oestrogen replacement therapy within previous 9 to 12 months, therapy with any other drug that affect skeleton like steroids, anti convulsants and anticoagulants.<br><br>Age: 56 (8.9) years<br><br>Time since menopause: NR<br><br>BMI: 26.4 (4.7) kg/m$^2$<br><br>Lumbar spine BMD: 0.85 (0.13) g/cm$^2$, femoral neck BMD: NR<br><br>Lumbar spine T-score: -2.7 (1.2), femoral neck T-score: NR<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: India<br><br>Race: NR |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 35 mg once weekly<br><br>2. Strontium ranelate 2 mg/day<br><br>(All participants received daily calcium 1000 mg and vitamin D 1000 IU.) |
| Outcomes | None of the outcomes of interest were reported except for gastrointestinal adverse events. However, the events were not reported by groups so the data were not extracted. Details were described in Table 1, Appendix 5. |
| Notes | Funding information: NR. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "In this randomised controlled trial study, 190 patients were divided into two groups."<br>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 but very likely an open-label study in which two treatments have different dose schedules (daily verse weekly). The participants' and personnel's performance were likely influenced by their knowledge of the assigned treatments. |
| Blinding of outcome assessment (detection bias) | Unclear risk | None of objective outcomes of interest, fracture outcomes, was reported. |

**Narula 2012** *(Continued)*

| | | |
|---|---|---|
| Objective outcomes | | |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | Blinding was not mentioned but very likely an open-label study in which two treatments have different dose schedules (daily verse weekly). The assessment of the subjective outcomes was likely influenced by the participants' and assessor's knowledge of the assigned treatments. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | Only one safety outcome of interest, gastrointestinal adverse events, was reported. However, the event numbers were not provided and data were not extractable. |
| Selective reporting (reporting bias) | Unclear risk | Protocol was not available. In Treatment section, it reads: "Patients were questioned at each visit adverse events including minor complaints". However, only gastrointestinal adverse events were narratively described in discussion without quantitative numbers. It was not clear whether selective reporting existed. |
| Other bias | Low risk | It appeared to be free of other risks of bias. |

**NCT00365456**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Multi-centre, randomised and active-controlled trial<br>Secondary prevention<br>Duration: one year<br>Blinding: open-label<br>Trial completion: 245/268 (91%)<br>Risedronate: 127/132 (96%)<br>Parathyroid hormone (PTH 1-84): 118/136 (87%) |
| Participants | Inclusion criteria: Women above the age of 50 years with the diagnosis of postmenopausal (more than 5 years) primary osteoporosis, with a lumbar spine T score < -3.0 SD (at lumbar spine L1-L4, with a minimum of two evaluable vertebrae); have a life expectancy of >3 years; able to self-inject PTH (1-84), (or to have PTH (1-84) injection by a helper)<br>Exclusion criteria: NR<br>Age: 64.0 (7.4) years<br>Time since menopause: NR<br>BMI: 24.1 (3.8) kg/m$^2$<br>Lumbar spine BMD: NR, femoral neck BMD: NR<br>Lumbar spine T-score: -3.62 (0.47), femoral neck T-score: NR<br>Prevalent vertebral fractures: 66/268 (25%) |

**NCT00365456** *(Continued)*

| | |
|---|---|
| | Previous bisphosphonate experience: 268/268 (100%)<br><br>Source: Denmark<br><br>Race: white (80%), Black (10%), Asian (5%), and other (5%) |
| Interventions | 1) Risedronate (orally): 35 mg tablet once weekly.<br><br>2) PTH 1-84 (sc): Self-administered parathyroid hormone100 µg in a volume of 71.4 µL daily as a subcutaneous injection in the abdomen using the Preotact pen.<br><br>Run-in: In Period I, all participants received PTH(1-84) treatment for 1 year; in Period II, all received risedronate for 1 year. |
| Outcomes | None of the fracture outcome data were extracted.<br><br>Withdrawals due to adverse events: ascertainment was not specified. |
| Notes | 1. Funded by Takeda.<br><br>2. PEAK Trial, trial registry number: NCT00365456.<br><br>3. This trial was divided into 3 consecutive open-label treatment phases of 12 months with randomisation after Trial Period II. Data were extracted from period III.<br><br>4. Full publication was not found and data were extracted from the protocol registered website. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Allocation: Randomized"<br>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 | Study was described as "open-label", treatments have different routes of medication administration: subcutaneous injection and oral use. The participants and personnel were likely influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the objective outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | Study was described as "open-label", treatments have different routes of medication administration; subcutaneous injection and oral use. The subjective outcomes might have been influenced by the participants', investigators', or assessors' knowledge of the allocated interventions if the blinding was not conducted. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the objective outcome data were extracted for analysis. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Only one safety outcome, withdrawal due to adverse event, was extracted.All randomised participants were included and it seems to be at low risk of bias. |
| Selective reporting (reporting bias) | Unclear risk | Full publication of this trial was not found and all of the data were extracted from the protocol registered website: clinicaltrials.gov. However, in the proto- |

**NCT00365456** *(Continued)*

| | | |
|---|---|---|
| | | col section, the primary and secondary outcomes were not described. It was not clear if the reported outcomes followed what the original protocol had planned. |
| Other bias | Unclear risk | All information and data were extracted from clinical trial registry website, which did not report the adverse events separately by treatment phase. The study materials of the study were brief and not scrutinised by peer review process. It was not clear if any important bias would have been introduced. |

**NCT02063854**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomized, phase II/III, parallel group comparative study<br>Secondary prevention<br>Duration: 12 months<br>Blinding: double-blind<br>Trial completion: 750/871 (86%)<br>Risedronate immediate-release (IR) 2.5 mg/day on awakening: 178/199 (89%)<br>Risedronate delayed-release (DR) 25 mg/month on awakening: 54/66 (82%)<br>Risedronate DR 25 mg/month, following breakfast: 176/206 (85%)<br>Risedronate DR 25 mg/month, 30 minutes after breakfast:58/68 (85%)<br>Risedronate DR 37.5 mg/month on awakening: 54/65 (83%)<br>Risedronate DR 37.5 mg/month, following breakfast: 170/201 (86%) |
| Participants | Exclusion criteria: with secondary osteoporosis; with diseases (other than secondary osteoporosis) that present with decreased bone mass; with findings that affects the measurement of mean bone mineral density of the lumbar spine by dual-energy X-ray absorptiometry (DXA); with a history of radiotherapy to the lumbar spine or the pelvis; planning to receive surgical dental procedures such as tooth extraction (including dental implant treatment) during the treatment period; with a history of treatment with any anti-receptor activator of nuclear factor-κB ligand (RANKL) monoclonal antibodies or parathyroid hormone products within 1 year before the start of the treatment period; with a history of treatment with any bisphosphonate products within 24 weeks before the start of the treatment period; having received any drugs that affect bone metabolism within 8 weeks before the start of the treatment period; with disorders such as oesophagitis, peptic ulcer (e.g. oesophageal ulcer, gastric ulcer, and duodenal ulcer), or gastrointestinal bleeding; with disorders that delay oesophageal emptying (e.g. dysphagia, oesophagostenosis, or achalasia of the oesophagus); with hypocalcaemia, hypercalcaemia, a diagnosis of renal calculus, serious renal, hepatic, or cardiac disease; having received surgical dental procedures, such as a tooth extraction (including dental implant treatment), but whose dental problems remain unresolved at the start of the treatment period.<br>Age: 68.9 (2.2) years<br>Time since menopause: 18.7 (2.2) years<br>BMI: 21.9 (1.0) kg/$m^2$<br>Lumbar spine BMD: 0.66 (0.22) g/$cm^2$, femoral neck BMD: 0.53 (0.22) g/$cm^2$<br>Lumbar spine T-score: -2.98 (0.51), femoral neck T-score: -2.86 (0.31) |

**NCT02063854** *(Continued)*

| | |
|---|---|
| | Prevalent vertebral fractures: 339/871 (39%)<br><br>Previous bisphosphonate experience: 98/871 (11%)<br><br>Source: Japan<br><br>Race: Asian (100%) |
| Interventions | Six-arm comparison:<br><br>1. NE-58095 immediate release (IR) 2.5 mg/day at time of wakening + three NE-58095 delayed release (DR) placebo-matching tablet once monthly, each taken at time of wakening, following breakfast, and 30 minutes after breakfast.<br><br>2. NE-58095 DR 25 mg/month at time of wakening + two NE-58095 DR placebo-matching tablets, once monthly, each taken following breakfast and 30 minutes after breakfast + NE-58095 IR placebo-matching tablet, once daily, at time of wakening.<br><br>3. NE-58095 DR 25 mg tablet/month, following breakfast + two NE-58095 DR placebo-matching tablet once monthly, each taken 30 minutes after breakfast and at time of wakening + NE-58095 IR placebo-matching tablet, once daily, at time of wakening.<br><br>4. NE-58095 DR 25 mg/month, 30 minutes after breakfast + two NE-58095 DR placebo-matching tablet once monthly, each taken following breakfast and at time of wakening + NE-58095 IR placebo-matching tablet, once daily, at time of wakening.<br><br>5. NE-58095 DR 37.5 mg/month, at time of wakening + two NE-58095 DR placebo-matching tablet, once monthly, each taken following breakfast and 30 minutes after breakfast+ NE-58095 IR placebo-matching tablet, once daily, at time of wakening.<br><br>6. NE-58095 DR 37.5 mg/month, following breakfast + two NE-58095 DR placebo-matching tablet, once monthly, each taken 30 minutes after breakfast and at time of wakening + NE-58095 IR placebo-matching tablet, once daily, at time of wakening.<br><br>(Participants were required to take calcium lactate hydrate 195 mg/day, after dinner.) |
| Outcomes | Radiographic vertebral fractures were assessed as secondary outcome. New non-traumatic vertebral fractures were identified by interpretable X-ray images of 13 vertebrae from the fourth thoracic to the fourth lumbar vertebra by a enteral review committee member. The X-ray images were visually inspected and classified into normal (Grade 0), mild deformation (Grade 1), moderate deformation (Grade 2), or severe deformation (Grade 3). If the assessment of any vertebra became worse by at least 1 grade after starting the treatment, its height was measured. A new vertebral fracture or a worsening pre-existing vertebral fracture was concluded if the vertebra's height was reduced from the baseline by at least 20% and by at least 4 mm.<br><br>Clinical vertebral fractures were assessed as safety outcome, in addition to serious adverse events and withdrawals due to adverse events. Safety was monitored during the study with the recording of clinical and laboratory adverse events. |
| Notes | 1. Funded by Takeda.<br><br>2. Trial Registry Number: NCT02063854. Full publication was not found and data were extracted from the protocol registered website.<br><br>3. This study was not included in the quantitative synthesis because all pair-wise comparisons of risedronate included unapproved doses. Details were provided in Table 3, Appendix 5. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Participants with a diagnosis of involutional osteoporosis were randomised at a ratio of 3:1:3:1:1:3:1 into 1 of 7 treatment groups: once-daily |

**NCT02063854** *(Continued)*

| | | |
|---|---|---|
| | | NE-58095 2.5 mg immediate release (IR) or once-monthly NE-58095 25 mg or 37.5 mg delayed release (DR) on awakening, after breakfast or 30 minutes following breakfast.'<br>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) | Low risk | Quote: "A Phase II/III, Double-blind, Parallel Group Comparative Study ..."<br>A double-dummy method was adopted with the use of matched-placebos. The blinding methods were judged appropriate to prevent performance bias. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | The blinding methods were judged appropriate to prevent detection bias, especially for objective outcomes which require clinical evidence and professional judgement. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | The blinding methods were judged appropriate to prevent detection bias from subjective outcomes assessment. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Radiographic and clinical vertebral fracture (RVF and CVF) were reported. Relevant statistical approach was not provided.<br>For RVF, 93% (806/871) who had received at least 1 dose of study drug and had data available for analyses were included; while for CVF, all participants, except one not receiving medication, were included.<br>Overall, 86% (750/871) of the randomised participants completed the 12-month study, with the numbers and reasons of early discontinuation being balanced across groups. It was judged to be at low risk of bias given the completion rates, with which the portion of missing data would not significantly bias the estimate. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Two safety outcomes, withdrawals due to adverse events and serious adverse events, were reported. Relevant statistical approach was not provided. Only the participants receiving medications were included in the analysis. It was judged to be at low risk of bias given the high completion rates and equally withdrawals across groups. |
| Selective reporting (reporting bias) | Low risk | No peer-reviewed publication of this study was found. However, the reported outcomes seemed to be consistent with those listed in the registry record. |
| Other bias | Unclear risk | All the study information were extracted from the clinical trial registry website. It was not clear if the study was subject to other risk of bias. |

**Ohtori 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised controlled trial<br>Secondary prevention<br>Blinding: open-label<br>Duration: one year<br>Trial completion: 62/62 (100%) |

**Ohtori 2013** *(Continued)*

| | |
|---|---|
| | Risedronate: 20/20 (100%)<br><br>Teriparatide: 20/20 (100%)<br><br>Control: 22/22 (100%) |
| Participants | Inclusion criteria: all of the patients were diagnosed as having osteoporosis on the basis of Japanese criteria. Patients had low back and leg pain, continuing for at least 3 months. They were diagnosed with lumbar degenerative spondylolisthesis with spinal stenosis on radiography, magnetic resonance imaging, myelography, and computed tomography (CT) after myelography. Diagnosis of spondylolisthesis and inclusion criteria for fusion surgery were (1) more than 5% slip of vertebra in a neutral position or (2) more than 3 mm translation between flexion and extension positions on radiographic evaluation.<br><br>Exclusion criteria: patients who had previously undergone spinal surgery were excluded. We also excluded those patients having spinal tumour, infection, and trauma.<br><br>Age: 77.6 (6.0) years<br><br>Time since menopause: NR<br><br>BMI: NR<br><br>Lumbar spine BMD: NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: NR, femoral neck T-score: NR<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: Japan<br><br>Race: Asian (100%) |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 2.5 mg/day<br><br>2. Teriparatide 20 µg/day, SC<br><br>3. Control: no treatment |
| Outcomes | None of the fracture outcomes of interest were reported.<br><br>Serious adverse events and withdrawals due to adverse events: Participant's safety was monitored and incidents were reported as adverse events. |
| Notes | No funds were received in support of this work. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Quote: "Randomization to a Teriparatide, Risedronate, or Control Group...Patients were divided into 3 groups: the first serial 22 patients were allocated to a control group without medication for osteoporosis, the next serial 20 patients were allocated to a risedronate group, and the final 20 patients were allocated to a teriparatide group. "<br>It was a randomisation trial. However, the reported approach to generating treatment sequence was not by random. |

**Ohtori 2013** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | High risk | As above, the treatment assignment was by the serial. Both the investigators and participants could anticipate which treatment was assigned. |
| Blinding of participants and personnel (performance bias) | High risk | Quote: "... the operating surgeon was not blinded as to which treatment arm the patients were in..."<br><br>In addition, blinding was not mentioned and it was probably open-label because of the different regimen (no treatment versus oral use versus daily subcutaneous injection of the study drugs).<br><br>It was 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 bias their performance. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the fracture outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | As above, in this open-label study, the participants and assessors were not blinded, which would likely influence the assessment of subjective outcomes. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | Quote: "At final follow-up, there was no drop out of patients from any of the 3 groups. "<br>Two safety outcomes of interest, withdrawal due to adverse events and serious adverse events, were extracted. All randomised participants were followed to the end of the study and included in the safety analysis. It was 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 method section. |
| Other bias | Low risk | It appeared to be free of other risks of bias. |

**Paggiosi 2014a**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: two years [including a 1-year extension. Thirty-nine participants (23%) left the study after 1-year treatment principally due to a delay in gaining approval to extend the study.]<br><br>Blinding: open-label<br><br>Trial completion: 1-year 142/172 (83%); 2-year 94/172 (55%)<br><br>Risedronate: 2-year 31/58 (53%)<br><br>Alendronate: 2-year 34/57 (60%)<br><br>Ibandronate: 2-year 29/57 (51%) |

**Paggiosi 2014a** *(Continued)*

| | |
|---|---|
| Participants | Inclusion criteria: women with postmenopausal osteoporosis, with either (i) a BMD T-score≤−2.5 at the lumbar spine or proximal femur (stratum 1) or (ii) a BMD T-score≤−1.0 at the lumbar spine or proximal femur plus a previous fracture sustained during a fall from standing height or less (stratum 2). Inclusion criteria specified that the women were >5 years postmenopausal but aged <85 years, ambulatory and willing and able to give informed consent.<br><br>Exclusion criteria: individuals taking medications (including calcium supplements in the last month or bisphosphonates in the past year) and/or diagnosed with diseases known to affect bone were not eligible to participate in the study. We excluded women who were morbidly obese (body mass index (BMI)> 35 kg/m2 ) or underweight (BMI<18 kg/m2 ) or those that had a sustained a fracture in the past year.<br><br>Age: 67.1 (7.2) years<br><br>Time since menopause: 18.6 (6.3) years<br><br>BMI: 26.4 (3.8) kg/$m^2$<br><br>Lumbar spine BMD: g/$cm^2$, femoral neck BMD: NR<br><br>Lumbar spine T-score: -2.23 (0.95), femoral neck T-score: NR<br><br>Prevalent vertebral fractures: 22/172 (13%)<br><br>Previous bisphosphonate experience: 4/172 (2%)<br><br>Source: United Kingdom<br><br>Race: NR |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 35 mg once a week<br><br>2. Alendronate 70 mg once a week<br><br>3. Ibandronate 150 mg once a month |
| Outcomes | Hip and clinical vertebral fractures: evaluated as adverse events: ascertainment was not specified and inferred as "0" from the text.<br><br>Serious adverse events, atypical femoral fractures, atrial fibrillation, and acute phase reaction: ascertainment was not specified. Incidents were reported as adverse events. |
| Notes | 1. Funded by Warner Chilcott<br><br>2. The TRIO study, registered with ClinicalTrials.gov (number NCT00666627) and with European Union Drug Regulating Authorities Clinical Trials (EudraCT, number 2006-004738-33). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...a 2-year, open-label, parallel randomised control trial... using a stratified block randomisation method, by Clinical Trials Pharmacists at Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. Study staff acquiring the physical bone measurements, investigators assessing clinical data and statisticians were all blinded to the medication code assignment."<br>However, the method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Low risk | As above, the sequence generation was produced by a third party and blind to the participants, investigators and outcome assessors. |

**Paggiosi 2014a** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias) | High risk | Quote: "...a 2-year, open-label, parallel randomised control trial of three orally administered bisphosphonates, at their licensed dose..."<br><br>It was an open-label study, in which the participants and personnel were not blinded. The different schedules of medications (daily versus monthly) would likely influence their mindset toward the medication so the performance bias might not be avoided. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | For the identification of fractures which were mainly based on clinical and objective criteria, the assessment was less likely influenced by the lack of blinding. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | It was judged to be at high risk of bias given that the assessment of subjective outcomes might be influenced by the participants' or assessors' knowledge of the allocated interventions after assignment. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: "We did not perform any statistical analyses on adverse events, but we did specify in advance events of special interest, and these included acute phase response, atrial fibrillation, conjunctivitis, dyspepsia and fracture....A total of 142 women on the three study drugs completed year 1; however, only 94 of these completed the whole of the 2-year study"<br>Fracture outcomes of interest were reported as safety outcomes and inferred as "0". It is not clear if all the randomised population were included in the analysis. The 2-year completion rates were 51% (29/57), 60% (34/57) and 53% (31/58) in ibandronate, alendronate and risedronate, respectively. It was judged to be at high risk of bias given the low completion rates, unknown reasons for the early discontinuations and the lack of methods of handling missing data. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | As above, It was judged to be at high risk of bias given the low completion rates, unknown reasons for the early discontinuations and the lack of methods of handling missing data. |
| Selective reporting (reporting bias) | Low risk | Protocol could be found in trial registration sites of https://clinicaltrials.gov/ct2/show/NCT00666627 and https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-004738-33/GB). The outcomes of interest were reported as described in the protocol. |
| Other bias | Unclear risk | Quote: "The reason for this large drop-out was principally a delay in gaining approval to extend the study from 1 to 2 years, and this resulted in 39 postmenopausal women leaving the study after 1 year of treatment...we extended the trial from 1 to 2 years, but because of delays with research governance procedures, we had to allow 39 patients to discontinue. "<br>It seemed that the second year extension was not pre-planed and amended after the study was launched. It was not clear how whether the change would have introduced bias of any kind. |

**Reginster 2000**

| ***Study characteristics*** | |
|---|---|
| Methods | Multinational, randomised, placebo-controlled trial<br><br>Secondary prevention<br><br>Duration: three years [The 2.5 mg/day group discontinued at 2 years due to protocol amendment. Two 2-year extensional periods (year 4 to 5 and year 6 to 7) were conducted.] |

**Reginster 2000** *(Continued)*

| | |
|---|---|
| | Blinding: double masked<br><br>Trial completion: 542/1226 (44%)<br><br>Risedronate 5 mg/day: 251/408 (62%)<br><br>Risedronate 2.5 mg/day: 70/410 (17%)<br><br>Placebo: 221/408 (54%) |
| Participants | Inclusion criteria: ambulatory women up to 85 years old who had been post menopausal at least 5 years. Minimum two radiographically confirmed vertebral T4-L4 fractures.<br><br>Exclusion criteria: conditions that could interfere with evaluation of spinal osteoporosis; receiving calcitonin, calcitriol or Vitamin D within one month, anabolic steroids, or HRT within 3 months, bisphosphonates, fluoride within 6 months.<br><br>Age: 71.0 (4.0) years<br><br>Time since menopause: 24.7 (5.0) years<br><br>BMI: NR<br><br>Lumbar spine BMD: 0.79 (0.15) g/cm$^2$, femoral neck BMD: 0.58 (0.17) g/cm$^2$<br><br>Lumbar spine T-score: -2.77 (0.82), femoral neck T-score: NR<br><br>Prevalent vertebral fractures: 1226/1226 (100%)<br><br>Previous bisphosphonate experience: NR<br><br>Source: 80 European and Australian centres<br><br>Race: NR |
| Interventions | Three-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Risedronate 2.5 mg/day<br><br>3. Placebo<br><br>(All participants received daily calcium 100 mg; patient would take vitamin D500 IU/day if baseline 25-hydroxyvitamin D levels were below 40 nmol/L.) |
| Outcomes | Radiographic vertebral and non-vertebra fractures were assessed as efficacy outcomes.<br><br>Radiographic vertebral fractures: lateral thoraco-lumbar T4-L4 spine radiographs were obtained at baseline, 1,2 and 3 years and were read in the order they were taken at a single radiology department. Prevalent and incident fractures were diagnosed quantitatively and semi-quantitatively. Quantitative assessment defined incident fracture as a 15% decrease of anterior, posterior or middle vertebral height in a vertebra that was normal at baseline. In the semi-quantitative assessment a new fracture was diagnosed if the grade changed from 0 (normal) to 1(mild) 2 (moderate), or 3 (severe). An independent radiologist adjudicated discrepancies between methods.<br><br>Non-vertebral, hip and wrist fractures: radiographically-confirmed fractures of the clavicle, humerus, wrist, pelvis, hip or leg, regardless of relationship to trauma.<br><br>Serious adverse events, withdrawals due to adverse events, gastrointestinal adverse events: participant's safety was monitored and incidents were reported as adverse events. |
| Notes | 1. Funding by Procter & Gamble Pharmaceuticals and Hoechst Marion Roussel<br><br>2. VERT multinational: the Vertebral Efficacy with Risedronate Therapy Study |

**Reginster 2000** *(Continued)*

3. Due to the protocol amendment, outcome data for 2.5 mg/day group was only available at year 1 and 2 (plotted from figure 1a-b). Outcome data for the extensional year 4 to 5 were not analysed and narratively discussed. Outcome data for the extensional year 6 to 7 were not usable because all the included participants received risedronate.

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: “This randomised ….” 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 | Quote: "...double-masked, placebo-controlled, parallel-group study..."<br><br>This was a double-blind study, but the blinding methods were not provided. Similarity of treatments was not reported and the early withdrawal of most participants from the 2.5 mg group may have broken the blinding of the participants and personnel. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "Radiographic assessments were made at the Department of Experimental Radiology, Erasmus University, and Rotterdam. Prevalent (baseline) and incident vertebral fractures were diagnosed quantitatively and semi-quantitatively…An independent radiologist adjudicated discrepancies between the methods….Other efficacy measures included radiographically confirmed non-vertebral osteoporosis-related fractures."<br><br>Although the effectiveness of the blinding was in question, the assessment of fractures were based on radiographic and clinical evidence, which was less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | As above, the effectiveness of the blinding was in question. It was judged to be at unclear risk of bias given that the assessments of subjective outcomes would possibly be influenced by the participants' reporting or assessors' knowledge of the allocated interventions. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Quote: “Analyses were performed on an intent-to-treat basis…”<br><br>In this 5-year study, the completion rates over the study period were:**1-year**, Placebo: 81% (330/407), Risedronate 2.5 mg/day: 81% (332/408), Risedronate 5 mg/day: 82% (333/407) **3-year**, Placebo: 54% (221/407), Risedronate 2.5 mg/day: 17% (70/408, 233 were withdrawal due to protocol amendment), Risedronate 5 mg/day: 62 % (251/407) 5-year, Placebo: 26% (104/407), Risedronate 2.5 mg/day: total withdrawal due to protocol amendment), Risedronate 5 mg/day: 28% (114/407) Except for the 1-year, the completion rates were way below 80% and there was no approach to handling the missing data, which would likely to introduce high risk of bias to the effect estimates. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | As above, the comparatively low completion rates across the years and groups and the lack of approach to handling the missing data would likely to introduce high risk of bias to the effect estimates. |
| 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 | 1. “The study duration was 3 years; the risedronate 2.5 mg group was discontinued after 2 years, because of other data showing that the 5 mg dose produced a more consistent effect in increasing BMD while having a similar safe- |

**Reginster 2000** *(Continued)*

| | |
|---|---|
| | ty profile to the 2.5 mg dose.“The group of risedronate 2.5 mg was terminated during the study period.<br><br>2. Outcome data for year 4 to 5 and year 6 to 7 was not usable so narratively discussed. |

**Reid 2006**

| ***Study characteristics*** | |
|---|---|
| Methods | Multi-centre, randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: two years [including a 1-year extension, and 85% (798/936) of the originally randomised entered the extension.]<br><br>Blinding: double-masked, double-dummy<br><br>Trial completion: 1-year 854/936 (91%); 2-year 716/936 (76%)<br><br>Alendronate: 1-year 424/468 (91%); 2-year 366/468 (78%)<br><br>Risedronate: 1-year 430/468 (92%); 2-year 350/468 (75%) |
| Participants | Inclusion criteria: community-dwelling, ambulatory, postmenopausal (≥ 6 months from cessation of menses) women ≥ 40 years of age (≥ 25 years if rendered menopausal surgically) with a BMD ≥ 2.0 SDs below young normal mean bone density (T< -2.0) in at least one of four sites [total hip, hip trochanter, femoral neck or posterior-anterior (PA) lumbar spine (L1-L4)]. The women were otherwise required to be in good general health, with hip and spinal anatomy suitable for dual-energy X-ray absorptiometry (DXA).<br><br>Exclusion criteria: with a history of abnormalities of the oesophagus that delay oesophageal emptying, such as stricture or achalasia, were excluded, as were those unable to remain upright for 30 minutes after dosing Women with hypocalcaemia, hypovitaminosis D [serum 25(OH)D < 10 ng/mL], or metabolic bone diseases other than postmenopausal osteoporosis also were excluded. Use of oestrogen, oestrogen analogues, tibolone or anabolic steroids within 6 months, any bisphosphonate within 1 year or for ≥ 2 years within 5 years, or any parathyroid hormone within the past year.<br><br>Age: 64.1 (8.2) years<br><br>Time since menopause: 16.8 (9.5) years<br><br>BMI: NR<br><br>Lumbar spine BMD: NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: -2.64 (0.87), femoral neck T-score: -2.12 (0.75)<br><br>Prevalent vertebral fractures:<br><br>Previous bisphosphonate experience: NR<br><br>Source: 75 centres in 27 countries in Europe, the Americas, and Asia-Pacific (UK, Canada, Italy, Brazil, France, USA, Australia)<br><br>Race: Caucasian (79%), Asian (8%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate: risedronate 35 mg once weekly + alendronate matching placebo |

**Reid 2006** *(Continued)*

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| | 2. Alendronate: alendronate 70 mg once weekly + risedronate matching placebo<br><br>(All participants received daily calcium 1000 mg and vitamin D 400 IU.) |
| Outcomes | None of the fracture outcomes of interest were extracted.<br><br>Withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events: Participant's safety was monitored and incidents were reported as adverse events.The ascertainment was not specified. |
| Notes | 1. Funded by a grant from Merck & Co., Inc.<br><br>2. Trial Name: FACT - International, Trial Registry: NCT00092040. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Assignment to treatment group was made using a computer-generated random allocation schedule generated by the study statistician. " |
| Allocation concealment (selection bias) | Low risk | Quote: "Numbered containers were used to implement allocation and each patient was assigned by the next number in the sequence upon being enrolled. All study personnel, including investigators, study-site personnel, patients, monitors, central laboratory and DXA facility personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers once recruitment, data collection and laboratory analyses were complete for the 1 year extension."<br><br>Sequentially-numbered containers were used. Double-dummy blinding. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "...randomly assigned to receive either alendronic acid 70 mg once weekly and risedronic acid matching placebo, or risedronic acid 35 mg once weekly and alendronic acid matching placebo....All study personnel, patients, monitors, central laboratory and DXA facility personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers once recruitment, data collection and laboratory analyses were complete for the 1-year extension."<br><br>Matching placebos of counter drug were used and the blinding were maintained. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the fracture outcomes of interest were extracted. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | Matching placebos of counter drug were used and the blinding were maintained. The assessment of the subjective outcomes were less likely influenced. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | In both year 1 and year-2 extension periods, all randomised participants were included in the safety analysis. In year 1, 91.9% (430/468) in alendronate group and 90.6% (424/468) in risedronate completed the study; in year 2, 90.8% (366/403) in alendronate group and 88.6% (350/395) in risedronate completed the study. It was judged to be at low risk of bias given that the completion |

**Reid 2006** *(Continued)*

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| | | rates were high, the small portion of the missing data would less likely to impact the estimation of effect sizes. |
| 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 extension (Protocol 907–10) was a double-blind, active-controlled, multicenter study during which all eligible women maintained their original randomised, blinded treatment allocation from year 1 (oral alendronate 70 mg OW or oral risedronate 35 mg for an additional 12 months. Seventy-two of the original 75 international sites chose to participate in the extension study."<br><br>Year 2 was an extension study and patients were offered the option to re-consent. This may have resulted in a higher loss of patients than a continuous trial. However, it was not clear whether and what kind of bias might have been introduced. |

**Rosen 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Multicentre, randomised and active-controlled trial<br><br>Primary prevention<br><br>Duration: one year + one-year extension [79% (833/1053 ) of the randomised entered the extension]<br><br>Blinding: double-masked, double-dummy<br><br>Trial completion: 1-year 892/1053 (85%); 2 year-708/1053 (67%)<br><br>Risedronate: 1-year 454/533 (85%); 2 year 333/533 (67%)<br><br>Alendronate: 1-year 438/520 (84%); 2 year 375/520 (72%) |
| Participants | Inclusion criteria: community-dwelling, ambulatory, postmenopausal (at least 6 months) women ≥ 40 years of age (≥ 25 years if surgically menopausal). Those who had low BMD, defined by a BMD of ≥2.0 SD below young normal mean bone mass in at least one of four sites (total hip, hip trochanter, femoral neck, or posterior-anterior [PA] lumbar spine [L1–L4]), based on the normative database of the manufacturer of the individual densitometer and who met pre-specified entry criteria were randomised and enrolled. ) Patients were otherwise required to be in good general health, with hip and spinal anatomy suitable for DXA.<br><br>Exclusion criteria: with a history of abnormalities of the oesophagus that delay oesophageal emptying, such as stricture or achalasia; unable to remain upright for 30 minutes after dosing; with hypocalcaemia (serum calcium < 8.5 mg/dL), hypovitaminosis D [serum 25(OH)D < 10 ng/mL], or metabolic bone diseases other than postmenopausal osteoporosis; if they had taken oestrogen, oestrogen analogues, tibolone, or anabolic steroids within 6 months; oestrogen use for 1 week at least 3 months before study entry was allowed, as was the use of vaginal oestrogen cream (2 g, up to two times weekly); prior use of any bisphosphonate within 1 year or for ≥2 years within 5 years; the use of any parathyroid hormone within the past year; Treatment with fluoride and treatment with glucocorticoids for >1 month with >7.5 mg of prednisone or its equivalent, daily within 6 months of randomisation, and treatment with immuno-suppressants were not allowed.<br><br>Age: 64.5 (9.8) years<br><br>Time since menopause: 18.5 (11.9) years<br><br>BMI: 25.4 (4.6) kg/m$^2$ |

**Rosen 2005** *(Continued)*

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| | Lumbar spine BMD: NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: -2.25 (0.95), femoral neck T-score: -2.14 (0.67)<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: USA<br><br>Race: Caucasian (95%), Black (1%), Asian (1%), and other (3%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate: risedronate 35 mg/week + alendronate-matching placebo once weekly<br><br>2. Alendronate: alendronate 70 mg/week + risedronate-matching placebo once weekly<br><br>[All participants received daily calcium 500 mg and vitamin D 400 IU, either from dietary sources or a supplement (Oscal 500 + D).] |
| Outcomes | Fractures were reported but not by anatomic location and group. None of the fracture outcome data were extracted.<br><br>Three safety outcomes, including withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events, were reported but the ascertainment was not specified. |
| Notes | 1. Funded by Aventis, Eli Lilly and Company, Merck, Novartis, NPC Pharmaceuticals, and Wyeth.<br><br>2. Trial Name: FACT - US, registry number: NCT00092014. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomised to one of two treatment groups using a computer-generated, blinded schedule provided by the sponsor. Patients and investigators were blinded to treatment."<br><br>The method of sequence generation was at random and appropriate. |
| Allocation concealment (selection bias) | Low risk | As above, allocation sequence was generated by the third party, which was independent from the research staff. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "... each patient received two bottles of study medication (one active and one placebo). Group 1 patients received alendronate 70 mg OW (Fosamax; Merck, Whitehouse Station, NJ, USA) and risedronate-matching placebo, whereas group 2 patients received risedronate 35 mg OW (Actonel; Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA) and alendronate-matching placebo. All study medications were taken with a full glass of water..."<br><br>Each drug's matching placebo was used and the same regimen were used. Blinding methods were judged appropriate to prevent possible performance bias from participants and personnel. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | Fractures were reported but not by anatomic location and group. None of the fracture outcome data were extracted. |

**Rosen 2005** *(Continued)*

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| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding methods were judged appropriate. The detection bias possibly occurring in the assessment of subjective outcomes could be effectively avoided. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of the efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | In FACT study: Quote: "The safety analysis included all patients who received at least one dose of study medication in either treatment group." In FACT extension: "All 825 women who received at least one dose of study medication in the extension were included in the safety analysis."<br>In alendronate and risedronate groups, 84.2% (438/820) and 85.2% (454/533) of the randomised participants completed and included in the safety analysis. However, in the 1-year extension period, 79% (833/1053) consented, among whom 99% received treatment and included in the safety analysis. The total withdrawal rates of the two groups in the extension period were unknown. Given the limited information, the data for upper gastrointestinal adverse events and serious adverse events was extracted from the overall 2 years; while the data for withdrawal due to adverse events from the 1-year. It was judged to be at high risk of bias given the unclear attrition and the lack of approach to handling the missing data. |
| Selective reporting (reporting bias) | Low risk | Protocol was not available; however, the outcomes of interest were reported as described in the method section in the main publications of main results and 1-year interim results. |
| Other bias | Low risk | It appears to be free of other risks of bias. |

**Roux 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Blinding: open-label<br>Trial completion: 824/870 (95%)<br>Risedronate: 402/435 (92%)<br>Denosumab: 422/435 (97%) |
| Participants | Inclusion criteria: ambulatory, postmenopausal women aged ≥55 years; had been previously prescribed alendronate therapy, with the first daily or weekly alendronate prescription ≥1 month prior to screening, having either stopped oral alendronate therapy before the screening visit or been still taking oral alendronate therapy (no washout period) with low adherence, which was assessed by a score of b6 on the Osteoporosis Specific Morisky Medication Adherence Scale (OS-MMAS).<br>Exclusion criteria: any prior or current treatment with osteoporosis medication other than daily or weekly oral alendronate therapy, hormone replacement therapy, and calcium and vitamin D (use of raloxifene or calcitonin prior to initiation of alendronate therapy was allowed); use of the following medications within 3 months of screening: tibolone, anabolic steroids or testosterone, and glucocorticosteroids (≥5 mg prednisone equivalent per day for >10 days or a total cumulative dose of ≥50 mg); |

**Roux 2014** *(Continued)*

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| | contraindicated or poorly tolerant of alendronate; significantly impaired renal function; previous participation in clinical trials with denosumab within the preceding 12 months regardless of treatment; reported malignancy within the last 5 years, except cervical carcinoma in situ or basal cell carcinoma; and any metabolic bone disease that had the potential to interfere with the interpretation of the findings. Vitamin D deficiency, defined as serum 25 (OH) vitamin D levels<20ng/mL, was an exclusion criterion: repletion as confirmed by a serum vitamin D level ≥20ng/mL was allowed and subjects were able to be re-screened only once.<br><br>Age: 67.8 (6.9) years<br><br>Time since menopause: 20.2 (8.9) years<br><br>BMI: NR<br><br>Lumbar spine BMD: NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: -2.2 (1.2), femoral neck T-score: -1.9 (0.7)<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: 840/870 (97%)<br><br>Source: 82 centres in Europe, Australia, and Canada<br><br>Race: Caucasian (98%), Asian (1%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate: risedronate (po) 150 mg once monthly<br><br>2. Denosumab: denosumab 60 mg, SC every 6 months<br><br>(All participants received daily calcium ≥1000 mg and vitamin D ≥800 IU.) |
| Outcomes | Clinical vertebral and hip fractures: ascertainment was not specific and reported as serious adverse events.<br><br>Withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events, osteonecrosis of the jaw, atypical femoral neck and atrial fibrillation: Incidents of adverse events and serious adverse events were collected throughout the study. |
| Notes | 1. Funded by Amgen Inc.<br><br>2. Trial registry number: NCT00919711. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomized, open-label, parallel-group study. Subjects were randomized 1:1 to receive either denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) or risedronate orally (PO) 150 mg once monthly (QM, one 75 mg tablet on each of 2 consecutive days) for 12 months."<br><br>Method for sequence generation was not provided. |
| Allocation concealment (selection bias) | Unclear risk | As above, method for sequence generation was not provided. |
| Blinding of participants and personnel (performance bias) | High risk | Quote: "open-label", "denosumab 60 mg subcutaneously (SC) every 6 months (Q6M) or risedronate orally (PO) 150 mg once monthly (QM, one 75 mg tablet on each of 2 consecutive days) for 12 months." |

**Roux 2014** *(Continued)*

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| | | The participants and personnel were not blinded. They were likely influenced by the different treatment drug delivery routes and schedules. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Although it lacked blinding, the assessment of fractures based on clinical and objective evidence were less likely influenced. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | As above, it lacked blinding in participants and personnel, which might influence the assessment of subjective (safety) outcomes. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Quote: "The safety analysis set included all randomised subjects who received ≥1 dose of investigational product."<br><br>Fractures were reported as adverse events. 1-year completion rate was 402/435 in risedronate group (92%) and 422/435 (97%) in denosumab group. Discontinuation due to AEs were 13 people in the risedronate group and 3 in the denosumab group (3 people). Safety analysis set included 858/870 (99%) of all randomised participants. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Low risk | As above, the safety analysis set included 858/870 (99%) randomised subjects who received ≥1 dose of investigational product. Total of 94.7% completed the study (92.4% in risedronate and 97% denosumab ) and the reasons were for discontinuation reported. It was judged to be at low risk of bias. |
| Selective reporting (reporting bias) | Low risk | No protocol was found but there was an NCT record. Fracture outcomes were mentioned descriptively in the publication and not specified by site and were unable to be extracted. In the NCT, they were listed under SAEs specified by site and were extracted. However, this was unlikely to be evidence of reporting bias because fractures were not a pre-specified outcome of the study and were only reported as adverse events. |
| Other bias | Low risk | No other sources of biases were observed. |

**Sarioglu 2006**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Blinding: single-blind<br><br>Duration: 12 months<br><br>Trial completion: NR/50<br><br>Risedronate: NR/25<br><br>Alendronate: NR/25 |
| Participants | Inclusion criteria: postmenopausal women with osteoporosis (T-score of less than -2.5).<br><br>Exclusion criteria: patients who were over 75 years and taking treatment for osteoporosis (i.e. estrogens, calcitonin, and anabolic steroids), who have the presence of any disease which interferes with bone metabolism (i.e. metabolic, inflammatory, hepatic, renal, malignant or immune disorders), or who have recent use of drugs known to affect bone metabolism and history of oesophagitis and peptic ulcer. |

**Sarioglu 2006** *(Continued)*

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| | Age: 58.8 (7.0) years<br>Time since menopause: 13.4 (2.8) years<br>BMI: 27.4(3.8) kg/m$^2$<br>Lumbar spine BMD: 0.90 (0.11) g/cm$^2$, femoral neck BMD: 0.77 (0.11) g/cm$^2$<br>Lumbar spine T-score: NR, femoral neck T-score: NR<br>Prevalent vertebral fractures: 5/50 (10%)<br>Previous bisphosphonate experience: NR<br>Source: Turkey<br>Race: NR |
| Interventions | Two-arm comparison:<br>1. Risedronate 5 mg/day<br>2. Alendronate 70 mg/week<br>(All women received daily calcium 1000 mg and Vitamin D 400 IU.) |
| Outcomes | Zero fractures for radiographic vertebral, non-vertebral, hip, wrist and atypical femoral fractures were inferred from the text Quote: "No other fractures were detected throughout the study period". All fracture outcomes were reported as safety outcomes.<br>Radiographic vertebral fractures: lateral and anteroposterior (AP) thoracic and lumbar spine radiographs were obtained at baseline and at 12th month, and were evaluated for vertebral fractures. The ascertainment for other fracture outcomes was not specified. |
| Notes | Funding information: NR |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "In this prospective, single-blind randomised study, 50 postmenopausal women with osteoporosis were included and randomized into two groups."<br>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 | Quote: "...single-blind randomised study...Lateral and anteroposterior (AP) thoracic and lumbar spine radiographs were obtained at baseline and at 12th month, and were evaluated for vertebral fracture."<br>Blinding approach was not provided and it was not known who was blinded. The two treatments had different dose schedules (daily versus monthly), and the participants and personnel were likely influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | Quote: "Lateral and anteroposterior (AP) thoracic and lumbar spine radiographs were obtained at baseline and at 12th month, and were evaluated for vertebral fracture." |

**Sarioglu 2006** *(Continued)*

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| | | Blinding approach was not provided. However, it is judged to be low risk of bias given that the assessment of objective outcomes were based on objective evidence and were less subject to ineffective blinding risk. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Unclear risk | No subjective outcome was assessed or reported. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | The primary outcome of this study seemed to be the change of bone mineral density after treatment. Fracture outcomes were reported as safety outcomes and inferred from Quote: " No other fracture was detected throughout the study period."<br><br>There was no information about the statistical analyses and attrition. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | As above, it was judged to be 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 method section. |
| Other bias | Low risk | It appeared to be free of other bias. |

**Tanaka 2017**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: two years<br><br>Blinding: open-label<br><br>Trial completion: 1333/1983 (67%)<br><br>Risedronate: 689/991 (70%)<br><br>Risedronate + Menatetrenone (Vitamin $K_2$): 644/992 (65%) |
| Participants | Inclusion criteria: postmenopausal women 65 years or older, had any of the risk factors suggested by the Adequate Treatment of Osteoporosis (A-TOP) research group, including age of 70 years or older, having one or more prevalent vertebral fractures between T4 and L4, BMD below minus three standard deviations of the young adult mean, and an unde rcarboxylated osteocalcin (ucOC) level of 4.5 ng/mL or more.<br><br>Exclusion criteria: prior treatment with warfarin; secondary osteoporosis or metabolic bone diseases other than osteoporosis; contraindication for administration of vitamin K2 and risedronate; hyperparathyroidism or hypoparathyroidism; mental disorders with the potential to result in unreliable self-reported data; prevalent vertebral fracture at six or more sites; severe degenerative deformation of the spine between T4 and L4; which may interfere with judgment of incident fracture or the precise measurement of lumbar BMD; critical disorders of the heart; liver; or kidney; and prior treatment with bisphosphonates within 6 months.<br><br>Age: 75.3 (5.8) years<br><br>Time since menopause: NR |

**Tanaka 2017** *(Continued)*

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|---|---|
| | BMI: 23.3 (3.8) kg/m$^2$<br>Lumbar spine BMD: NR; femoral neck BMD: NR<br>Lumbar spine T-score: -3.2 (1.6); femoral neck T-score: NR<br>Prevalent vertebral fractures: 1458/1874 (77.8%)<br>Previous bisphosphonate experience: NR<br>Source: Japan<br>Race: Asian (100%) |
| Interventions | Two-arm comparison:<br>1. Risedronate 2.5 mg/day or 17.5/week<br>2. Risedronate 2.5 mg/day or 17.5/week + Menatetrenone (Vitamin $K_2$) 45 mg/day<br>(Participants were not required to take supplemental calcium or vitamin D. ) |
| Outcomes | All fracture outcomes were reported as efficacy outcomes.<br>Radiographic vertebral fractures: anteroposterior and lateral radiographs of the thoracic and lumbar spine within 3 months before the date of informed consent, 1 month each before 6-, 12-, and 24-month visit were initially examined by investigators independent of the central committee according to the semi-quantitative method. After the first X-ray films had been collected, one evaluator for prevalent fractures or two independent evaluators for incident fractures, an orthopedist, and a radiologist reviewed those films simultaneously after the patient's information had been masked according to the same semi-quantitative method.<br>Non-vertebral, hip, wrist and atypical femoral fractures: all fractures excluding vertebral, facial, and skull fractures that had occurred after the age of 50 years were recorded. All incident non-vertebral fractures were assessed by radiographs at the time of fracture with the exception of vertebral, facial, and skull fractures. Information such as the date, site, and circumstance of the fracture was recorded simultaneously. After X-ray films taken at each institution had been collected, they were reviewed by two independent evaluators.<br>Three safety outcomes, including withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events, were reported but the ascertainment was not specified. |
| Notes | 1. Funded by the Public Health Research Foundation<br>2. Trial name: Japanese Osteoporosis Intervention `Trial-03` (JOINT-03). University Hospital Medical Information Network Clinical Trials Registry identification number: UMIN000000991. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Random allocation was implemented by a Web-based computerized system for the modified minimization method that adjusts that data for an imbalance in eight factors: age, number of prevalent vertebral fractures, bone mineral density (BMD), serum ucOC level, presence of alcohol intake, past or current smoking, history of parents' femoral neck fracture, and institution." |
| Allocation concealment (selection bias) | Low risk | Quote: "The algorithm for random allocation was concealed from the investigators and patients". |

**Tanaka 2017** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias) | High risk | The study was an quote: "open-labelled, randomised trial."<br><br>Blinding was not conducted and the participants and personnel were likely influenced. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Low risk | As above, however it reads "assessors for fractures (objective outcomes) were "assessors were completely blinded to treatment assignment."<br><br>Although blinding was not conducted, the assessment for objective outcomes was done by a blinded assessor and based on the clinical evidence. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | Since adverse events may have been reported by the patients, subjective outcomes may have been more likely to be affected by lack of blinding. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | The 2-year completion rates are 69% in the risedronate and vitamin K2 group, and 73% in the risedronate alone group. The overall completion rate, given the randomised population, is 67% (1333/1983). The approach to handling missing data were not provided. |
| Incomplete outcome data (attrition bias) Safety Outcomes | High risk | The 2-year completion rates were 69% in the risedronate and vitamin K2 group, and 73% in the risedronate alone group. Except for withdrawals due to adverse events which had all randomised participants accounted for and had similar incidence between arms (31 among 992 in combination group versus 18 among 991 in risedronate group), other two safety outcomes, serious adverse events and gastrointestinal adverse events, were judged to be at high risk of bias given the attrition and the lack of approach to handling missing data. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting was found, and the protocol (Tanaka 2013) was published before the study results. |
| Other bias | Low risk | No other risk of bias was found. |

**Välimäki 2007**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, placebo-controlled trial<br><br>Primary prevention<br><br>Duration: 24 months<br><br>Blinding: double-blind<br><br>Trial completion: NR/171<br><br>Risedronate: NR/114<br><br>Placebo: NR/57 |
| Participants | Inclusion criteria: healthy, ambulatory, late-postmenopausal (≥ 5 years from menopausal) women who had a baseline LS BMD T-score between -2.5 and -1 SD or the presence of ≥ 1 other risk factor for osteoporosis or the presence of hip osteopenia.<br><br>Exclusion criteria: women who had a history of cancer within the 5 years before the study, any condition that might interfere with the evaluation of LS BMD (e.g. confluent aortic calcifications, severe osteoarthritis, spinal fusion or ≥ 2 fractured lumbar vertebrae [L1-L4]), or any disease requiring long-term |

**Välimäki 2007** *(Continued)*

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|---|---|
| | treatment with systemic corticoids, or who had received bisphosphonate therapy (any dosage) within 6 months of starting the study treatment or for ≥14 days within a year before the start of the study.<br><br>Age: 65.9 (6.8) years<br><br>Time since menopause: 18.3 (7.9) years<br><br>BMI: 25.4 (3.7) kg/$m^2$<br><br>Lumbar spine BMD: NR, femoral neck BMD: NR<br><br>Lumbar spine T-score: -1.82 (0.42), femoral neck T-score: -1.23 (0.58)<br><br>Prevalent vertebral fractures: NR<br><br>Previous bisphosphonate experience: NR<br><br>Source: Finland, the Netherlands, Norway, Spain, Sweden<br><br>Race: Caucasian (100%) |
| Interventions | Two-arm comparison:<br><br>1. Risedronate 5 mg/day<br><br>2. Placebo<br><br>(All women received a daily supplement containing 1000 mg of elemental calcium and 400 IU of vitamin D.) |
| Outcomes | Fracture were reported as safety outcome, including clinical vertebral, non-vertebral, hip, wrist and atypical femoral fractures. However, ascertainment was not specified.<br><br>Withdrawals due to adverse events, serious adverse events and gastrointestinal adverse events: Participant's safety was monitored and incidents were reported as adverse events. |
| Notes | 1. Funded by the Alliance for Better Bone Health (Procter & Gamble and Sanofi Aventis).<br><br>2. Trial Registry Number: NCT00353080. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Enrolled patients received risedronate 5 mg* or an identical placebo PO (tablet) QD in a 2:1 ratio according to a predefined randomization schedule."<br><br>However, the methods of how the randomisation schedule was made was not provided. |
| Allocation concealment (selection bias) | Unclear risk | The method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "…double-blind, placebo-controlled, parallel-group…Enrolled patients received risedronate 5 mg* or an identical placebo PO (tablet) "<br><br>Matching (identical) placebos were used. The participants and personnel were effectively blinded and the performance bias from them could be prevented. |
| Blinding of outcome assessment (detection bias) | Low risk | As above, the blinding method was judged appropriate, so the assessment of objective outcomes were less likely biased. |

**Välimäki 2007** *(Continued)*

| | | |
|---|---|---|
| Objective outcomes | | |
| Blinding of outcome assessment (detection bias) Subjective outcomes | Low risk | As above, blinding approach was appropriate, so the assessment of subjective outcomes were less likely biased. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Quote: "Occurrences of clinical vertebral and non-vertebral fractures were noted in the AE reports..All patients treated with ≥ 1 dose of study medication were included in the tolerability analyses, with patients grouped according to the treatment they received."<br><br>Incident fractures were recorded as safety outcome. However, in the 24-month study, attrition data were not provided, although all the randomised participants were included in the analysis, except for 1 not taking any medication. It was not clear whether the portion of missing data and the approach to handling it would bias the outcome estimates. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | As above, the attrition data were not provided. Although all the randomised participants were included in the analysis, except for 1 not taking any medication, it was not clear how much the attrition was and how it influenced the results. The information available was insufficient to make a judgment. |
| 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 appeared to be free of other risks of bias. |

**Yanik 2008**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Randomised and active-controlled trial<br><br>Secondary prevention<br><br>Duration: one year<br><br>Blinding: NR<br><br>Trial completion: 127/150 (85%) (150 participants were included, but only 127 were reported.)<br><br>Risedronate: 44/NR (NR)<br><br>Alendronate: 47/NR (NR)<br><br>Raloxifene: 36/NR (NR) |
| Participants | Inclusion criteria: according to World Health Organization, T-score <=-2.5 were accepted as osteoporosis; patients has been in menopause for a year or whose last menopause is not definite with serum Follicle Stimulated Hormone (FSH) and serum oestrodiol levels in the postmenopausal range; did not receive medication due to osteoporosis during the month; under 75 years of age<br><br>Exclusion criteria: osteoporosis metabolic diseases, cancer stories and menopause patients with severe vegetative symptoms, deep vein thrombosis, myocardial infarction, cerebrovascular event story present, abnormality of glucose and lipid metabolism those who use drugs related to these diseases, hypertension, renal and hepatic disorders, thyroid-related diseases those using drugs or corticosteroids, severe oesophageal disease. Those with hypocalcaemia were excluded from the scope of the study. |

**Yanik 2008** *(Continued)*

| | |
|---|---|
| | Age: 62.8 (6.8) years<br>Time since menopause: 17.7 (2.3) years<br>BMI: 24.6 kg/m$^2$<br>Lumbar spine BMD: 0.83 (0.10) g/cm$^2$, femoral neck BMD: 0.74 (0.12) g/cm$^2$<br>Lumbar spine T-score: -2.76 (0.73), femoral neck T-score: -1.78 (1.03)<br>Prevalent vertebral fractures: NR<br>Previous bisphosphonate experience: NR<br>Source: NR<br>Race: NR |
| Interventions | Three-arm comparison:<br>1. Risedronate 35 mg once weekly<br>2. Alendronate 70 mg once weekly<br>3. Raloxifene 60 mg/day<br>(All participants received daily calcium 1200 mg and vitamin D 800 IU.) |
| Outcomes | None of the fracture outcome of interest was reported.<br>Serious adverse events: ascertainment was not specified, and probably monitored as safety outcome. |
| Notes | 1. Funding information: NR<br>2. The publication is in Turkish and was translated by online Google Translate Service. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The participants were randomized into three groups using a random number table..."<br>A random number table was used, which was appropriate. |
| Allocation concealment (selection bias) | Unclear risk | The method for allocation concealment was not provided. |
| Blinding of participants and personnel (performance bias) | High risk | Blinding and placebo were not mentioned and it was probably an open-label trial because of the different regimen (weekly versus daily use of the study drugs). It was judged to be at high risk of bias given the open-label design where the participants and personnel might have known the allocated intervention, would bias their performance. |
| Blinding of outcome assessment (detection bias) Objective outcomes | Unclear risk | None of the objective outcomes of interest were reported. |
| Blinding of outcome assessment (detection bias) Subjective outcomes | High risk | Blinding and placebo were not mentioned and it was probably an open-label trial because of the different regimen (weekly versus daily use of the study drugs). It is judged to be at high risk of bias given the open-label design where the participants' and assessors' knowledge about the allocated interventions would bias the assessment of subjective outcomes. |

**Yanik 2008** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | None of efficacy outcome data were extracted. |
| Incomplete outcome data (attrition bias) Safety Outcomes | Unclear risk | Statistical methods for safety analysis were not provided. Only one safety outcome of interest, serious adverse events, was extracted. Unclear if all the randomised participants were included in the analysis, because the number of patients randomised in each group was not mentioned. The one-year overall completion rate was 85% (127/150) but the dropout rates by groups were unknown. It was not clear if there were differential attrition between treatment groups. |
| Selective reporting (reporting bias) | Unclear risk | Protocol was not available. Only data for serious adverse events was extracted from "serious side effects"(as translated). It was not clear whether both meant the same.<br><br>It was not clear whether the outcomes were reported consistently with those described in the methods section. |
| Other bias | Unclear risk | All the information was translated by online translate program (Google translate, https://translate.google.ca/)). It was not clear if any important bias would have been introduced. |

**AEs:** adverse events;**BMD:** Bone mineral density;**BMI:** Body mass index; **FSH:** follicle stimulating hormone; **HRT:** Hormone replacement therapy; **NSAID:** Non-steroidal anti inflammatory drugs;**PTH:** parathyroid hormone; **WHO:** World Health Organization.
Participant characteristics: unless otherwise specified, participant characteristics were presented as mean (SD). **RCT:** randomised controlled trial; **SD:** standard deviation.
Route of drug administration: Unless otherwise specified, drugs were administered orally.
**IM:** intramuscular injection; **IU:** International units; **IV:** intravenous injection; **NR:** not reported;**SC:** subcutaneous injection.

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

| Study | Reason for exclusion |
|---|---|
| Adachi 2001 | Less than 1 year duration |
| Altintas 2007 | Less than 1 year duration |
| Anastasilakis 2008b | Less than 1 year duration |
| Article in Dutch 2001 | Study design (not RCT) |
| Bahlous 2009 | Less than 1 year duration |
| Bala 2013 | Companion record to included study but with no additional outcome |
| Borah 2004 | Companion record to included study but with no additional outcome |
| Borah 2005 | Companion record to included study but with no additional outcome |
| Borah 2010 | Companion record to included study but with no additional outcome |
| Borah 2010a | Companion record to included study but with no additional outcome |
| Brown 2014 | Study design (not RCT) |

| Study | Reason for exclusion |
|---|---|
| Caffarelli 2010 | Intervention/Comparator not of interest |
| Carlino 2011 | Population (does not exclusively include postmenopausal women) |
| Chapurlat 2011 | Companion record to included study but with no additional outcome |
| Chung 2009 | Less than 1 year duration |
| D'Amelio 2008 | Less than 1 year duration |
| Dane 2008 | Less than 1 year duration |
| Delmas 2007 | Intervention/Comparator not of interest |
| Dufresne 2003 | Companion record to included study but with no additional outcome |
| Duque 2009 | Study design (not RCT) |
| Duque 2011 | Companion record to included study but with no additional outcome |
| Durchschlag 2006 | Companion record to included study but with no additional outcome |
| Eastell 2003 | Companion record to included study but with no additional outcome |
| Eastell 2010 | Study design (not RCT) |
| Eastell 2011 | Intervention/Comparator not of interest |
| Eastell 2013 | Companion record to included study but with no additional outcome |
| Eriksen 2002 | Companion record to included study but with no additional outcome |
| Fujita 2009 | Population (does not exclusively include postmenopausal women) |
| Geusens 2017 | Companion record to included study but with no additional outcome |
| Goa 1998 | Study design (not RCT) |
| Gonnelli 2006 | Intervention/Comparator not of interest |
| Gossiel 2010 | Less than 1 year duration |
| Gossiel 2016 | Companion record to included study but with no additional outcome |
| Gossiel 2018 | Companion record to included study but with no additional outcome |
| Hadji 2011 | Companion record to included study but with no additional outcome |
| Hadji 2011a | Companion record to included study but with no additional outcome |
| Hagino 2014 | Companion record to included study but with no additional outcome |
| Harris 1999a | Companion record to included study but with no additional outcome |
| Hofbauer 2013 | Companion record to included study but with no additional outcome |

| Study | Reason for exclusion |
|---|---|
| Hongo 2015 | Less than 1 year duration |
| Hooper 1999 | Companion record to included study but with no additional outcome |
| Hosking 2009 | Study design (not RCT) |
| Iizuka 2008 | Intervention/Comparator not of interest |
| Ilter 2006 | Less than 1 year duration |
| Imai 2017 | Companion record to included study but with no additional outcome |
| Iwamoto 2016 | Less than 1 year duration |
| Kanis 2005 | Study design (not RCT) |
| Karadag-Saygi 2011 | Less than 1 year duration |
| Kendler 2009 | Study design (not RCT) |
| Kendler 2017 | Companion record to included study but with no additional outcome |
| Kushida 2004 | Population (does not exclusively include postmenopausal women) |
| Lanza 2000 | Less than 1 year duration |
| Lanza 2000a | Less than 1 year duration |
| Licata 1997 | Study design (not RCT) |
| Masud 2009 | Companion record to included study but with no additional outcome |
| Maugeri 2005 | Study design (not RCT) |
| McClung 1996 | Companion record to included study but with no additional outcome |
| McClung 1998 | Companion record to included study but with no additional outcome |
| McClung 2010a | Companion record to included study but with no additional outcome |
| McClung 2010b | Companion record to included study but with no additional outcome |
| McClung 2010c | Companion record to included study but with no additional outcome |
| McClung 2011 | Companion record to included study but with no additional outcome |
| Mellstrom 2004 | Companion record to included study but with no additional outcome |
| Miller 1999 | Companion record to included study but with no additional outcome |
| Miller 1999a | Population (does not exclusively include postmenopausal women) |
| Minisola 2019 | Companion record to included study but with no additional outcome |
| Ohtori 2012 | Less than 1 year duration |

| Study | Reason for exclusion |
|---|---|
| Oktem 2008 | Less than 1 year duration |
| Oliveira 2015 | Less than 1 year duration |
| Oral 2015 | Less than 1 year duration |
| Paggiosi 2014b | Companion record to included study but with no additional outcome |
| Palomba 2005 | Population (does not exclusively include postmenopausal women) |
| Pawlowski 2015 | Less than 1 year duration |
| Peris 2013 | Less than 1 year duration |
| Racewicz 2007 | Less than 1 year duration |
| Ralston 2011 | Intervention/Comparator not of interest |
| Recker 2011 | Companion record to included study but with no additional outcome |
| Recker 2015 | Study design (not RCT) |
| Reginster 2001 | Study design (not RCT) |
| Reszka 1999 | Study design (not RCT) |
| Ribot 1999 | Companion record to included study but with no additional outcome |
| Roux 2004 | Study design (not RCT) |
| Roux 2013 | Companion record to included study but with no additional outcome |
| Sebba 2004 | Study design (not RCT) |
| Seeman 2010a | Companion record to included study but with no additional outcome |
| Seibel 2004 | Study design (not RCT) |
| Shiraki 2003 | Less than 1 year duration |
| Singer 1995 | Study design (not RCT) |
| Ste-Marie 2009 | Less than 1 year duration |
| Stovall 2010 | Study design (not RCT) |
| Sunyecz 2009 | Study design (not RCT) |
| Takada 2007 | Less than 1 year duration |
| Tanaka 2014 | Companion record to included study but with no additional outcome |
| Taquet 1996 | Companion record to included study but with no additional outcome |
| Thomson 2002 | Less than 1 year duration |

| Study | Reason for exclusion |
|---|---|
| Watts 1998 | Study design (not RCT) |
| Watts 1999 | Companion record to included study but with no additional outcome |
| Watts 2003 | Companion record to included study but with no additional outcome |
| Watts 2008 | Intervention/Comparator not of interest |
| Zegels 2001 | Less than 1 year duration |
| Zerbini 2017 | Companion record to included study but with no additional outcome |
| Zoehrer 2006 | Companion record to included study but with no additional outcome |

**RCT:** randomised controlled trial.

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

#### Benhamou 2013

| | |
|---|---|
| Methods | Multicentre, randomised controlled, parallel-group trial<br>Primary or secondary prevention, indecisive for insufficient information<br>Duration: 12 months<br>Blinding: open-label<br>Trial completion: NR<br>Risedronate: NR<br>Denosumab: NR |
| Participants | Inclusion criteria: postmenopausal women aged >=55 years who were suboptimally adherent to ALN (discontinued ALN therapy or had an OSMMAS score of < 6).<br>Exclusion criteria: NR |
| Interventions | 1) Risedronate 150 mg once monthly<br>2) Denosumab 60 mg, SC every 6 months |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR<br>2. This was a conference abstract. |

#### Bilek 2016

| | |
|---|---|
| Methods | Randomised controlled trial<br>Primary prevention<br>Duration: 12 months |

**Bilek 2016** *(Continued)*

| | |
|---|---|
| | Trial completion: NR<br><br>Risedronate: NR<br><br>Control: NR<br><br>Exercise: NR |
| Participants | Inclusion criteria: women in first 5 years of menopause; BMD T score between -1.0 and -2.49 at total hip or L1-L4 spine (osteoporosis); 19 years of age or older; Healthcare provider's permission to be in study.<br><br>Exclusion criteria: BMO T Score < -2.5 at hip or spine (osteoporosis); Increased hip and major fracture based on FRAX score; bisphosphonates in last 6 months; currently on oestrogen, tamoxifen, aromatase Inhibitors, others; weight > 300 pounds; Serum Vitamin D 100 ng/mL; Any conditions that prohibit optimal CaD, risedronate, or exercise. |
| Interventions | 1) Risedronate 150 mg, every four weeks<br><br>2) Bone-loading exercise program, three times weekly<br><br>3) Control<br><br>(All participants received calcium citrate supplements to make the total daily intake (dietary and supplemental) ~1200 mg. They were prescribed doses of vitamin D based on their serum 25(OH) D levels at baseline, and make the goal of reaching a serum level of at least 30 ng/mL. ) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: The National Institute of Nursing Research of the National Institutes of Health under award number R01NR015029.<br><br>2. This was a protocol of Heartland Osteoporosis Prevention Study (HOPS), trial registry number: NCT02186600. |

**Deng 2020**

| | |
|---|---|
| Methods | Randomised controlled trial<br><br>Secondary prevention<br><br>Duration: 12 months<br><br>Blinding: open-label<br><br>Trial completion: NR/140<br><br>Risedronate: NR/70<br><br>Risedronate + Raloxifene: NR/70 |
| Participants | Inclusion criteria: a) Patients aged between 55 and 65 years old, with at least a 5-year interval from last menopause; b) Patients who were diagnosed according to the diagnostic criteria of osteoporosis by WHO, i.e. T ≤-2.5 for diagnosis.<br><br>Exclusioncriteria: a) Patients with the history of bone metabolism disease; b) Patients with the medication history of drugs affecting the bones or metabolism, such as diphosphonate, calcium or Vitamin D; c) Patients with deficiency in Vitamin D; d) Patients with problems in sexual hormones, or the history of hormone replacement therapy; e) Patients with the coagulopathy or thromboembolic diseases; f) Patients with cardiovascular diseases or cerebrovascular diseases; g) Patients |

**Deng 2020** *(Continued)*

| | |
|---|---|
| | with the history of drug abuse, smoking or alcohol, or the adverse responses or effect of drugs during the study; h) Patients that were unable to continue on the study. |
| Interventions | 1) Risedronate 5 mg daily<br>2) Risedronate 5 mg/day + Raloxifene 60 mg/day<br>[All participants were instructed to take outdoor exercise 1 to 2 hours per day and have balanced diet (taking food rich in calcium and low in salt, with appropriate volume of protein, and guaranteeing the daily intake of vitamin D at about 10μg (400 IU).] |
| Outcomes | None of the fracture outcomes of interest were reported.<br>Gastrointestinal symptoms were narratively described but the data were not extractable. |
| Notes | 1. Eligible study identified in the update search of 24 March, 2021.<br>2. Funding information: NR |

**Felsenberg 2010**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled trial<br>Primary prevention<br>Duration: 12 months<br>Trial completion: NR/159<br>Risedronate: NR<br>Placebo: NR |
| Participants | Inclusion criteria: osteopenic women, age 45-55 years and within 36 months from menopause.<br>Exclusion criteria:: NR |
| Interventions | 1) Risedronate 35 mg once weekly<br>2) Placebo<br>(Background medication: NR.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding was provided by Alliance for Better Bone Health (Warner Chilcott PLC and Sanofi-Aventis US, Inc).<br>2. This was a conference abstract. |

**Hagino 2014**

| | |
|---|---|
| Methods | Phase III, multicentre, randomised, parallel, active comparator controlled trial<br>Secondary prevention<br>Duration: 12 months |

**Hagino 2014** *(Continued)*

| | |
|---|---|
| | Blinding: double-blind<br><br>Trial completion: 745/851 (88%)<br><br>Risedronate 2.5 mg/day: 381/429 (89%)<br><br>Risedronate 75 mg/month: 364/422 (86%) |
| Participants | Inclusion criteria: ambulatory Japanese male and female participants aged ≥50 years who were diagnosed with osteoporosis, based on the criteria for primary osteoporosis of the Japanese Society for Bone and Mineral Research. Primary osteoporosis was defined by the presence of a fragility fracture and BMD < 80% of the 'young adult mean' (20 to 44 years of age), or BMD < 70% of the 'young adult mean' in the absence of a detectable fragility fracture. In the case of female participants, ≥2 years must have passed since menopause.<br><br>Exclusion criteria: factors which affect efficacy evaluation; secondary osteoporosis and any other disease causing decreased bone mass or affecting lumbar spine BMD (including severe scoliosis of the spine, fracture or severe deformation in any of the L2–L4 lumbar vertebrae, or a spinal X-ray image suggesting severe bone sclerosis [calcification] in any of the $L_2$–$L_4$ lumbar vertebrae); administration of bisphosphonate within 24 weeks before the first dose of the study drug; administration of any drug affecting bone metabolism such as selective oestrogen receptor modulators (SERMs), vitamin $D_3$ and vitamin $K_2$ preparations, and calcitonin analogs, etc. within 8 weeks before the first dose of the study drug; any patient judged by the attending physician to be unsuitable to participate in the study. |
| Interventions | 1) Risedronate 2.5 mg/day<br><br>2) Risedronate 75 mg/month |
| Outcomes | All reported outcome data, including radiographic vertebral, non-vertebral, and atypical femoral fractures, withdrawals due to adverse events, serious adverse events, gastrointestinal adverse events and acute phase reaction, were not extractable because 2% (13/849) of the participants were males and incidents were not separately reported. |
| Notes | 1. Eligible study identified in the update search of 24 March, 2021.<br><br>2. This study was supported by the Joint Development Program of Ajinomoto Pharmaceuticals Co., Ltd. and Takeda Pharmaceutical Company Limited. |

**Ia Vilariño 2009**

| | |
|---|---|
| Methods | Randomised controlled trial<br><br>Primary or secondary prevention, indecisive for insufficient information<br><br>Duration: 12 months<br><br>Trial completion: NR/122<br><br>Risedronate: NR/31<br><br>Alendronate 10 mg/day: NR/69<br><br>Alendronate 5 mg/day: NR/22 |
| Participants | Inclusion criteria: NR, but participants were described with average 62 years old, last period was in 76% of patients between 40-50 years old, and BMI was 24.<br><br>Exclusion criteria: NR |

**Ia Vilariño 2009** *(Continued)*

| | |
|---|---|
| Interventions | 1) Risedronate 5 mg/day<br>2) Alendronate 10 mg/day<br>3) Alendronate 5 mg/day<br>(Background medication: NR.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR<br>2. This was a conference abstract. |

**Lim 2019**

| | |
|---|---|
| Methods | Randomised, open-label trial<br>Primary or Secondary prevention, indecisive for insufficient information<br>Duration: four years<br>Trial completion: 90/223 (40%)<br>Risedronate: 54/114 (47%)<br>HRT: 36/109 (33%) |
| Participants | Inclusion criteria: NR, but the participants were described as "postmenopausal Korean women after hip fracture surgery".<br>Exclusion criteria:: NR |
| Interventions | 1) Risedronate 35 mg/week<br>2) HR = percutaneous 17-estradiol gel (0.1%, 1.5 gm/day) plus oral micronised progesterone (100 mg/day)<br>(All participants received daily calcium supplement, but the dose was not reported. ) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR<br>2. This was a conference abstract. |

**Matsuzaki 2012**

| | |
|---|---|
| Methods | Randomised and double-blind trial<br>Primary or secondary prevention, indecisive for insufficient information<br>Duration: 2 years<br>Trial completion: 67/184 (36%)<br>Risedronate: 18/NR |

**Matsuzaki 2012** *(Continued)*

| | |
|---|---|
| | Alfacalcidol: 13/NR<br>Risedronate + Alfacalcidol: 19/NR<br>Raloxifene + Alfacalcidol: 17/NR |
| Participants | Inclusion criteria: NR, but the participants were postmenopausal women (mean age 69.9 years old) with BMD < 80%-YAM<br>Exclusion criteria:: NR |
| Interventions | 1) Risedronate<br>2) Alfacalcidol<br>3) Risedronate + Alfacalcidol<br>4) Raloxifene + Alfacalcidol<br>Dose regimen for four groups: NR<br>(All participants received daily calcium 1000 mg) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR.<br>2. This was a conference abstract. |

**NCT00345644**

| | |
|---|---|
| Methods | Parallel and randomised controlled trial<br>Primary prevention<br>Duration: 24 months<br>Blinding: double-blind<br>Trial completion: NR (estimated enrolment: 156 participants)<br>Risedronate: NR<br>Placebo: NR |
| Participants | Inclusion criteria:: 0steopenic, postmenopausal women, between 55 and 75 years of age with a body mass index (BMI) < 30 kg/m$^2$<br>Exclusion criteria: clinical or radiological evidence of osteoporosis; Severe renal impairment; Serum 5-hydroxy vitamin D level < 15 ng/mL; history of recent primary hyperparathyroidism or recent thyroid disorder; history of any generalised bone disease; current use of glucocorticoids, estrogens, progestins, calcium supplements > 1 g/day, vitamin D supplements > 800 IU/day, parathyroid hormone (PTH), or any bisphosphonate for > 1 month at any time within the past 6 months. |
| Interventions | 1) Risedronate 35 mg/week<br>2) Placebo weekly<br>(Background medication was not reported.) |
| Outcomes | None of the outcomes of interest were reported. |

**NCT00345644** *(Continued)*

| | |
|---|---|
| Notes | 1. Eligible study (registered protocol) identified in the update search of 24 March, 2021. Study was completion in June 2009 but no results were posted.<br><br>2. Funding information: NR |

**NCT00386360**

| | |
|---|---|
| Methods | Randomised controlled trial<br><br>Primary prevention<br><br>Duration: 12 months<br><br>Blinding: quadruple masking (participant, care provider, investigator and outcome assessor)<br><br>Trial completion: 135/161 (84%)<br><br>Risedronate: 95/112 (85%)<br><br>Placebo: 40/49 (82%) |
| Participants | Inclusion criteria: cessation of menstruation (surgical or natural) between 6 and 36 months prior to study enrolment; osteopenic; must have at least 1 evaluable radius and tibia, without history of fracture (traumatic or atraumatic); BMI (body mass index) between 18 kg/$m^2$ and 28 kg/$m^2$ inclusive;<br><br>Exclusion criteria: history of any generalised bone disease, including hyperparathyroidism, Paget's disease of bone, renal osteodystrophy, or any other acquired or congenital bone disease; or any known condition that would interfere with the assessment of DXA (dual-energy X-ray absorptiometry) at either the lumbar spine (3 non-evaluable lumbar vertebrae at lumbar spine L1 - L4) or the femoral neck; clinical or radiological evidence of osteoporosis, such as atraumatic vertebral compression fracture (* 20% reduction in anterior-to-posterior or middle-to-posterior height ratio; or 20% reduction of the anterior, middle, and/or posterior height as compared with the adjacent vertebrae) documented by spinal X ray or a history of osteoporosis-related atraumatic fracture of the hip or of the wrist; glucocorticoid-induced osteopenia; previous bisphosphonate therapy. |
| Interventions | 1) Risedronate 35 mg/week<br><br>2) Placebo |
| Outcomes | None of the fracture outcome data of interest was reported.<br><br>Two and one, two and four and seven and five participants in risedronate and placebo group experienced non-vertebral fractures, withdrawals due to adverse events and serious adverse events, respectively. |
| Notes | 1. Sponsored by Warner Chilcott.<br><br>2. Eligible study identified in the update search of 24 March, 2021. |

**NCT00402441**

| | |
|---|---|
| Methods | Multicentre, randomised, placebo-controlled, and parallel group trial<br><br>Primary prevention<br><br>Duration: 12 months |

**NCT00402441** *(Continued)*

| | |
|---|---|
| | Blinding: double-blind<br>Trial completion: NR/260<br>Risedronate: NR<br>Placebo: NR |
| Participants | Inclusion criteria: postmenopausal for 0.5-5 years. Menopause is defined as 12 months without menses, based on medical history. women who were postmenopausal secondary to bilateral oophorectomy must have serum FSH >40 mIU/mL and estradiol < 20 pg/mL; with 3 contiguous lumbar spine vertebral bodies (L1-L4) without fracture or degenerative disease; and lumbar spine BMD mean value > 0.772 g/cm$^2$ (Hologic) or > 0.880 g/cm$^2$ (Lunar).<br>Exclusion criteria: participants with adequate lumbar spine BMD but osteoporotic by total proximal femur BMD (<0.637 g/cm$^2$ [Hologic]) or <0.694 g/cm$^2$ [Lunar]) as determined by dual-energy x-ray absorptiometry (DXA). |
| Interventions | 1) Risendronate 35 mg once a week<br>2) Placebo, weekly<br>(Background medication was not reported.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Eligible study (registered protocol) identified in the update search of 24 March, 2021. Study was completed in June 2004, but no results were posted.<br>2. Sponsor: Sanofi and Procter and Gamble (collaborator). |

**NCT00790101**

| | |
|---|---|
| Methods | Multi-centre, parallel and randomised controlled trial<br>Primary prevention<br>Duration: 18 months<br>Blinding: double-blind<br>Trial completion: NR (actual enrolment: 6 participants)<br>Risedronate: NR<br>Raloxifene: NR<br>Placebo: NR |
| Participants | Inclusion criteria: postmenopausal, ambulatory females; "postmenopausal" defined as the absence of menses for at least 12 continuous months); In general good health as determined by medical history, physical examination, and laboratory tests; LS spine BMD T-score between -1.0 and -2.4, inclusive; at least one analysable BMD site at both the hip (left or right) and LS spine (at least 3 measurable lumbar spine vertebrae; without fracture or sufficient degenerative disease); currently receiving no medications for the treatment or prevention of osteoporosis; had been on continuous HRT for at least 1 year prior to enrolment (The HRT must have ended within 18 months prior to the baseline visit, and the patient must have been off HRT medication for at least 3 months at the time of baseline visit,); patients rendered menopausal by surgical procedures between the ages of 55 and 65 years. |

**NCT00790101** *(Continued)*

| | |
|---|---|
| | Exclusion criteria: a history of cancer within 10 years prior to entry into the study, except for relatively "benign" and cured skin cancers such as basal and squamous cell carcinoma; a history of hyperparathyroidism, hyperthyroidism, osteomalacia, or other metabolic bone disease within one year prior to enrolment; any condition or disease that may interfere with the evaluation of at least 3 lumbar vertebrae (not necessarily contiguous), determined in a screening radiograph by a radiologist at the central facility (e.g., confluent aortic calcifications, severe osteoarthritis, spinal fusion, lumbar spine fractures); evidence of clinically significant organic or psychiatric disease on history or physical examination, which in the opinion of the investigator would prevent the patient from completing the study; markedly abnormal pretreatment laboratory finds that, in the opinion of the investigator, would prevent the patient from completing the study; a history of using any of the following medications prior to starting study: any bisphosphonate therapy, selective oestrogen receptor modulators (SERMs), parathyroid hormone, fluorides, calcitonin, calcitriol (>1.5 mcg/week), corticosteroids on a chronic basis for period ≥ 3 months; received a depot injection of >10,000 IU Vitamin D in the past 12 months; serum creatinine >1.6 mg/dl; unable to sit or stand upright for 30 minutes after taking the morning dose of risedronate; a history of recurrent nephrolithiasis or one episode of nephrolithiasis within 1 year of study entry, deep vein thrombosis or other coagulation disorders severe hepatic insufficiency; a history of hypersensitivity to raloxifene, risedronate, or to drugs with similar chemical structures; clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult; had one or more vertebral fractures after completing thoracic and LS spine films; and have experienced a low impact fracture related to osteopenia within two years of baseline visit. |
| Interventions | 1) Risedronate 35 mg/week<br>2) Raloxifene 60 mg/day<br>3) Placebo, dosing schedule not reported.<br>(Background medication was not reported.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Eligible study (registered protocol) identified in the update search of 24 March, 2021. Study was terminated (date unknown) and no results were posted.<br>2. Sponsor: Sanofi |

**NCT01904110**

| | |
|---|---|
| Methods | Parallel and randomised controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Blinding: open-label<br>Trial completion: NR/196<br>[Risedronate + Cholecalciferol], monthly: NR<br>[Risedronate + Cholecalciferol], weekly: NR |
| Participants | Inclusion criteria: female osteoporosis patients over 19 years of age (with menopause). The definition of osteoporosis included a BMD T-score ≤ -2.5 or less at mean Lumbar spine (L1~L4), femoral neck or total, or evidence of at least one vertebral fracture. The definition of menopause can be one of three conditions: spontaneous amenorrhoea for 12months, spontaneous amenorrhoea with serum FSH (follicle stimulating hormone) ≥ 40 mlIU/mL for 6months, or 6 weeks after bilateral ovariectomy whether hysterectomy of not. Patients who can be treated with oral bisphosphonate |

**NCT01904110** *(Continued)*

| | |
|---|---|
| | drugs; who have adequate to be measured DXA(Dual energy x-ray absorptiometry); who made a voluntary agreement after explanation of this study; patients who participated in clinical trial (H-L_RSNP_401) must have taken the Risenexplus and finish the study for 12 months.<br><br>Exclusion criteria: patients with oesophagus disorder; administered with osteoporosis therapy (except calcium,vitamin D medication) within previous 3 months; with serum calcium concentrations < 8.0 mg/dL; with severe nephropathy(serum creatinine> double of normal level; or unable to sit upright or stand 30 minutes. |
| Interventions | 1) [Risendronate+Cholecalciferol] combination in one tablet (Risenex M), once a month<br><br>2) [Risendronate/Cholecalciferol] combination in one tablet (Risenex Plus), once a week<br><br>(Background medication was not reported.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Eligible study (registered protocol) identified in the update search of 24 March, 2021. Study was completed 29 May, 2014 but no results were posted.<br><br>2. Sponsor: Hanlim Pharm. Co., Ltd. |

**Okamoto 2010**

| | |
|---|---|
| Methods | Randomised controlled trial<br><br>Primary or secondary prevention, indecisive for insufficient information<br><br>Duration: 1 year<br><br>Trial completion: NR/63<br><br>Risedronate: NR/33<br><br>Control: NR/30 |
| Participants | Inclusion criteria: patients with postmenopausal osteoporosis (diagnosis criteria were not provided).<br><br>Exclusion criteria: if had a disease or habit that may affect atherosclerosis and bone metabolism, such as smoking, diabetes mellitus, previous history of coronary and cerebral vascular accident, and severe impairment of activities of daily life (ADL); or with blood pressure of > 135/85 mmHg or serum LDL-cholesterol of > 150 mg/dL. |
| Interventions | 1) Risedronate 2. 5 mg/day<br><br>2) Control: nutritional supplements of calcium, vitamin D and vitamin K during the 1-year study period<br><br>(Background medication: NR.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | Funding information: NR |

**Pastore 2014**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Likely a secondary prevention, the relevant information was insufficient<br>Duration: 2 years (two-year teriparatide treatment prior to the randomisation)<br>Trial completion: 60/81<br>Risedronate: NR<br>Alendronate: NR<br>Ibandronate: NR<br>Strontium ranelate: NR<br>Placebo: NR |
| Participants | Inclusion criteria: NR, but the participants were described as "women with severe postmenopausal osteoporosis" (Diagnosis criteria were not provided. )<br>Exclusion criteria: NR |
| Interventions | 1) Risedronate, weekly + Teriparatide<br>2) Alendronate, weekly + Teriparatide<br>3) Ibandronate, monthly + Teriparatide<br>4) Strontium ranelate, daily + Teriparatide<br>5) Placebo + Teriparatide<br>Doses and routes of drug administration for the above drugs were not provided.<br>(All participants received calcium 1 g/day and vitamin D 5,600 IU/week.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR.<br>2. This was a conference abstract. |

**Seeman 2010**

| | |
|---|---|
| Methods | Double-blind, randomised controlled trial<br>Likely a primary prevention study, the relevant information was insufficient<br>Duration: 12 months<br>Trial completion: NR/159<br>Risedronate: NR<br>Placebo: NR |
| Participants | Inclusion criteria: NR, but the participants were described as "women with osteopenia aged 45-55 years within 36 months of menopause.".<br>Exclusion criteria:: NR |

**Seeman 2010** *(Continued)*

| | |
|---|---|
| Interventions | 1) Risedronate 35 mg/week<br>2) Placebo<br>(Background medication: NR.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR.<br>2. This was a conference abstract. |

**UMIN000010017**

| | |
|---|---|
| Methods | Randomised, active-controlled trial<br>Primary or secondary prevention, indecisive for insufficient information<br>Duration: NR<br>Blinding: open, but assessor(s) are blinded<br>Trial completion: 46 (Target sample size)<br>Risedronate: NR<br>Bazedoxifene: NR |
| Participants | Inclusion criteria: patients without osteoporosis therapy; postmenopausal women; non-smoker; patients who themselves can voluntarily provide written consent to participate in this study, and can also follow the study protocol.<br>Exclusion criteria: patients with vein thrombosis, anti-phospholipid antibody syndrome, severe hepatopathy or nephropathy that may affect the evaluation of drug safety, or patients who are deemed to be inappropriate by the investigator or sub-investigators. |
| Interventions | 1) Risendronate 2.5 mg, daily<br>2) Bazedoxifene 20 mg, daily<br>(Background medication was not reported.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Probably an eligible study (registered protocol) identified in the update search of 24 March, 2021. Study was terminated and no results were posted.<br>2. Investigator initiated and self-funded study. |

**Yeter 2014**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Primary prevention<br>Duration: 12 months<br>Trial completion: NR/90 |

**Yeter 2014** *(Continued)*

| | |
|---|---|
| | Risedronate: NR/29<br>Raloxifene: NR/30<br>Control: NR/31 |
| Participants | Inclusion criteria: patients with postmenopausal osteoporosis, with lumbar spine L1-L4 BMD average T-score less than -2; being in the postmenopausal period, and has given written consent prior to taking the study.<br>Exclusion criteria: systemic disease causing secondary bone loss, taken calcium and vitamin D, or any drug known to affect BMD at least 6 months prior to the study; has a history of active peptic ulcer or GIS bleeding; has active malignancy. |
| Interventions | 1) Risedronate 35 mg/week<br>2) Raloxifene 60 mg/day<br>3) Control<br>(All participants received daily calcium 1000 mg and vitamin D 400 IU.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | 1. Funding information: NR.<br>2. The study was published in Turkish and translated by online translation program (Google translate, https://translate.google.ca). |

**Yildirim 2005**

| | |
|---|---|
| Methods | Randomised controlled trial<br>Secondary prevention<br>Duration: 12 months<br>Trial completion: 188/200 (94%)<br>Risedronate: 47/50 (94%)<br>Alendronate: 47/50 (94%)<br>Salmon Calcitonin: 48/50 (96%)<br>Control: 46/50 (92%) |
| Participants | Inclusion criteria: women with postmenopausal osteoporosis, defined as a T score of = 2.5 SD below the mean value of controls according the World Health Organization (WHO)<br>Exclusion criteria: disorders of bone mineralisation, severe renal, hepatic, endocrine (Paget's disease, hyperthyroidism and hyperparathyroidism), haematological, lymphoproliferative, inflammatory and other malignant diseases, drug hypersensitivity, oesophagitis, peptic ulcer, history of radiotherapy to the lumbar spine or pelvis or use of drugs known to alter bone or calcium metabolism. Use of non-steroidal anti-inflammatory drugs and proton pump inhibitors was allowed. |
| Interventions | 1) Risedronate 5 mg/day<br>2) Alendronate 10 mg/day<br>3) Salmon calcitonin 200 IU/day, IN |

| | |
|---|---|
| **Yildirim 2005** *(Continued)* | (All participants received daily elemental calcium 1000 mg, in the form of calcium lactate, gluconate and calcium carbonate.) |
| Outcomes | None of the outcomes of interest were reported. |
| Notes | Funding information: NR |

**ADL:** activities of daily living; **BMD:** bone mineral density;**BMI:** body mass index; **HRT:** hormone replacement therapy; **IN:** intranasal;**IU:** international units**;IU: i**nternational units; **FSH:** follicle stimulating hormone; **GI:** gastrointestinal; **LDL: l**ow-density lipoprotein; **NR:** not reported; **sc:** subcutaneous injection;**SD:** standard deviation;**SERMS:** selective oestrogen receptor modulators; **WHO:** World Health Organization.
Participant characteristics: unless otherwise specified, participant characteristics were presented as mean (SD). **RCT:** randomised controlled trial; **SD:** standard deviation.
Route of drug administration: Unless otherwise specified, drugs were administered orally.
**IM:** intramuscular injection; **IN:** intranasal; **IU:** International units; **IV:** intravenous injection; **NR:** not reported;**SC:** subcutaneous injection.

## DATA AND ANALYSES

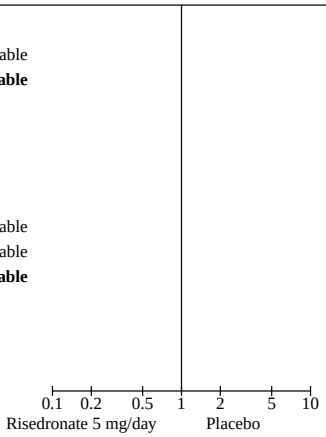
### Comparison 1. Risedronate 5 mg/day vs Placebo - Base case

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Clinical vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1.1 Clinical vertebral fractures, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 1.1.2 Clinical vertebral fractures, Secondary | 2 | 119 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 1.2 Non-vertebral fractures | 9 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.2.1 Non-vertebral Fractures, Primary | 3 | 497 | Risk Ratio (M-H, Fixed, 95% CI) | 0.54 [0.22, 1.35] |
| 1.2.2 Non-vertebral Fractures, Secondary | 6 | 12173 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.72, 0.90] |
| 1.3 Hip fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.3.1 Hip Fractures, Primary | 2 | 243 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 1.3.2 Hip Fractures, Secondary | 3 | 9450 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.56, 0.94] |
| 1.4 Wrist fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.4.1 Wrist Fractures, Primary | 2 | 243 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.03, 7.50] |
| 1.4.2 Wrist Fractures, Secondary | 3 | 1746 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.33, 1.24] |
| 1.5 Radiographic vertebral fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.5.1 Radiographic vertebral fractures, Primary | 2 | 327 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.42, 2.25] |
| 1.5.2 Radiographic vertebral fractures, Secondary | 3 | 2301 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.50, 0.75] |
| 1.6 Withdrawals due to adverse events | 11 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.6.1 Withdrawals due to adverse events, Primary | 3 | 748 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.38, 1.18] |
| 1.6.2 Withdrawals due to adverse events, Secondary | 8 | 9529 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.90, 1.07] |
| 1.7 Serious adverse events | 8 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.7.1 Serious adverse events, Primary | 2 | 424 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.42, 1.30] |
| 1.7.2 Serious adverse events, Secondary | 6 | 9435 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.94, 1.07] |
| 1.8 Gastrointestinal adverse events | 8 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.8.1 Gastrointestinal adverse events, Primary | 2 | 424 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.66, 1.44] |
| 1.8.2 Gastrointestinal adverse events, Secondary | 6 | 9434 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.93, 1.08] |
| 1.9 Atypical femoral fracture | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.9.1 Atypical femoral fracture, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 1.9.2 Atypical femoral fracture, Secondary | 2 | 1383 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

## Analysis 1.1. Comparison 1: Risedronate 5 mg/day vs Placebo - Base case, Outcome 1: Clinical vertebral fractures

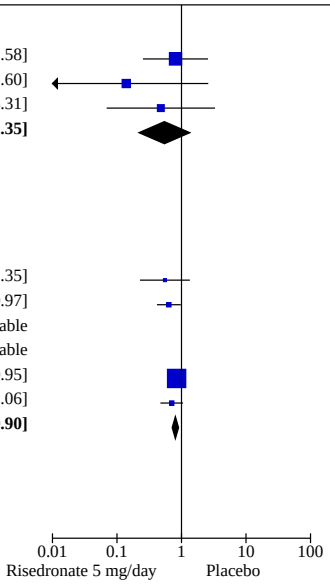
| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **1.1.1 Clinical vertebral fractures, Primary** | | | | | | | |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **115** | | **55** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |
| **1.1.2 Clinical vertebral fractures, Secondary** | | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable | ? ? + + + + + |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable | ? ? + + + + + |
| **Subtotal (95% CI)** | | **59** | | **60** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: 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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 2: Non-vertebral fractures

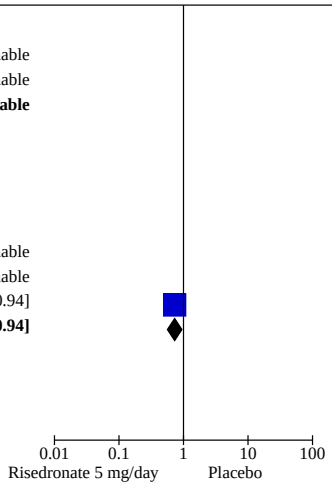
| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **1.2.1 Non-vertebral Fractures, Primary** | | | | | | | |
| Hooper 2005 | 5 | 129 | 6 | 125 | 49.4% | 0.81 [0.25 , 2.58] | + + + + - + + |
| Mortensen 1998 | 0 | 37 | 3 | 36 | 28.7% | 0.14 [0.01 , 2.60] | ? ? + + + + + |
| Välimäki 2007 | 2 | 115 | 2 | 55 | 21.9% | 0.48 [0.07 , 3.31] | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **281** | | **216** | **100.0%** | **0.54 [0.22 , 1.35]** | |
| Total events: | 7 | | 11 | | | | |
| Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.31 (P = 0.19) | | | | | | | |
| **1.2.2 Non-vertebral Fractures, Secondary** | | | | | | | |
| Fogelman 2000 | 7 | 140 | 13 | 144 | 2.2% | 0.55 [0.23 , 1.35] | ? ? - + - + ? |
| Harris 1999 | 33 | 812 | 52 | 815 | 8.9% | 0.64 [0.42 , 0.97] | + + + + - + ? |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable | ? ? + + + + + |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable | ? ? + + + + + |
| McClung 2001 | 583 | 6197 | 351 | 3134 | 80.1% | 0.84 [0.74 , 0.95] | ? ? + + - - + |
| Reginster 2000 | 36 | 406 | 51 | 406 | 8.8% | 0.71 [0.47 , 1.06] | ? ? - + - + ? |
| **Subtotal (95% CI)** | | **7614** | | **4559** | **100.0%** | **0.80 [0.72 , 0.90]** | |
| Total events: | 659 | | 467 | | | | |
| Heterogeneity: Chi² = 2.70, df = 3 (P = 0.44); I² = 0% | | | | | | | |
| Test for overall effect: Z = 3.75 (P = 0.0002) | | | | | | | |




**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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 3: Hip fractures

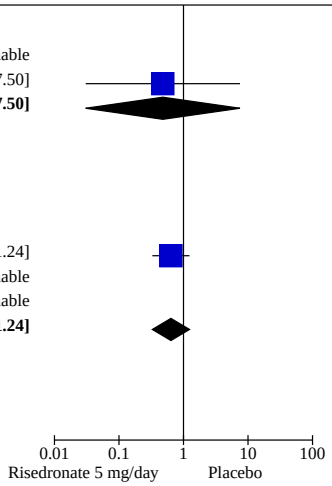
| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **1.3.1 Hip Fractures, Primary** | | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable | ? ? + + + + + |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **152** | | **91** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |
| **1.3.2 Hip Fractures, Secondary** | | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable | ? ? + + + + + |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable | ? ? + + + + + |
| McClung 2001 | 137 | 6197 | 95 | 3134 | 100.0% | 0.73 [0.56 , 0.94] | ? ? + + - - + |
| **Subtotal (95% CI)** | | **6256** | | **3194** | **100.0%** | **0.73 [0.56 , 0.94]** | |
| Total events: | 137 | | 95 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 2.40 (P = 0.02) | | | | | | | |




**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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 4: Wrist fractures

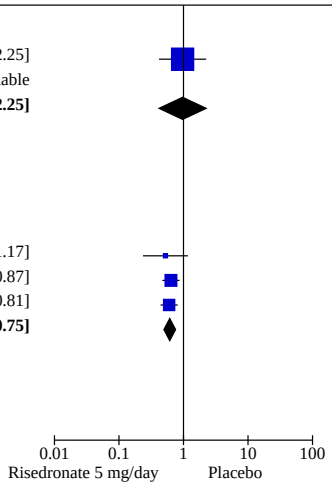
| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **1.4.1 Wrist Fractures, Primary** | | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable | ? ? + + + + + |
| Välimäki 2007 | 1 | 115 | 1 | 55 | 100.0% | 0.48 [0.03 , 7.50] | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **152** | | **91** | **100.0%** | **0.48 [0.03 , 7.50]** | |
| Total events: | 1 | | 1 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.53 (P = 0.60) | | | | | | | |
| **1.4.2 Wrist Fractures, Secondary** | | | | | | | |
| Harris 1999 | 14 | 812 | 22 | 815 | 100.0% | 0.64 [0.33 , 1.24] | + + + + - + ? |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable | ? ? + + + + + |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable | ? ? + + + + + |
| **Subtotal (95% CI)** | | **871** | | **875** | **100.0%** | **0.64 [0.33 , 1.24]** | |
| Total events: | 14 | | 22 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.19) | | | | | | | |




**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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 5: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 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** | | | | | | | |
| Hooper 2005 | 10 | 129 | 10 | 125 | 100.0% | 0.97 [0.42 , 2.25] | + + + + - + + |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable | ? ? + + + + + |
| **Subtotal (95% CI)** | | **166** | | **161** | **100.0%** | **0.97 [0.42 , 2.25]** | |
| Total events: | 10 | | 10 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.94) | | | | | | | |
| **1.5.2 Radiographic vertebral fractures, Secondary** | | | | | | | |
| Fogelman 2000 | 8 | 112 | 17 | 125 | 8.1% | 0.53 [0.24 , 1.17] | ? ? - + - + ? |
| Harris 1999 | 61 | 696 | 93 | 678 | 47.3% | 0.64 [0.47 , 0.87] | + + + + - + ? |
| Reginster 2000 | 53 | 344 | 89 | 346 | 44.6% | 0.60 [0.44 , 0.81] | ? ? - + - + ? |
| **Subtotal (95% CI)** | | **1152** | | **1149** | **100.0%** | **0.61 [0.50 , 0.75]** | |
| Total events: | 122 | | 199 | | | | |
| Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0% | | | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | | | |

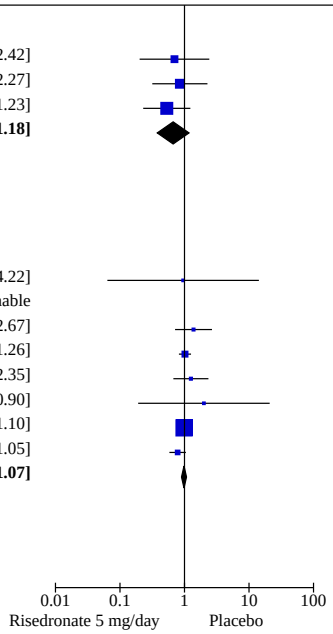


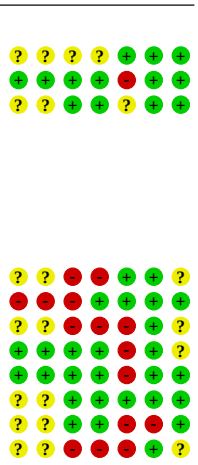

**Risk of bias legend**

(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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 6: Withdrawals due to adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 Withdrawals due to adverse events, Primary** | | | | | | |
| Bala 2014 | 6 | 221 | 4 | 103 | 21.2% | 0.70 [0.20 , 2.42] |
| Hooper 2005 | 7 | 129 | 8 | 125 | 31.5% | 0.85 [0.32 , 2.27] |
| Välimäki 2007 | 10 | 115 | 9 | 55 | 47.3% | 0.53 [0.23 , 1.23] |
| **Subtotal (95% CI)** | | **465** | | **283** | **100.0%** | **0.67 [0.38 , 1.18]** |
| Total events: | 23 | | 21 | | | |
| Heterogeneity: Chi² = 0.51, df = 2 (P = 0.77); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | | | |
| **1.6.2 Withdrawals due to adverse events, Secondary** | | | | | | |
| Dobnig 2006 | 1 | 21 | 1 | 20 | 0.1% | 0.95 [0.06 , 14.22] |
| Dundar 2009 | 0 | 41 | 0 | 20 | | Not estimable |
| Fogelman 2000 | 19 | 177 | 14 | 180 | 1.7% | 1.38 [0.71 , 2.67] |
| Harris 1999 | 138 | 813 | 136 | 815 | 16.7% | 1.02 [0.82 , 1.26] |
| Hosking 2003 | 31 | 222 | 12 | 108 | 2.0% | 1.26 [0.67 , 2.35] |
| Li 2005 | 2 | 30 | 1 | 30 | 0.1% | 2.00 [0.19 , 20.90] |
| McClung 2001 | 550 | 3104 | 564 | 3134 | 69.1% | 0.98 [0.89 , 1.10] |
| Reginster 2000 | 65 | 407 | 83 | 407 | 10.2% | 0.78 [0.58 , 1.05] |
| **Subtotal (95% CI)** | | **4815** | | **4714** | **100.0%** | **0.98 [0.90 , 1.07]** |
| Total events: | 806 | | 811 | | | |
| Heterogeneity: Chi² = 4.36, df = 6 (P = 0.63); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.38 (P = 0.70) | | | | | | |



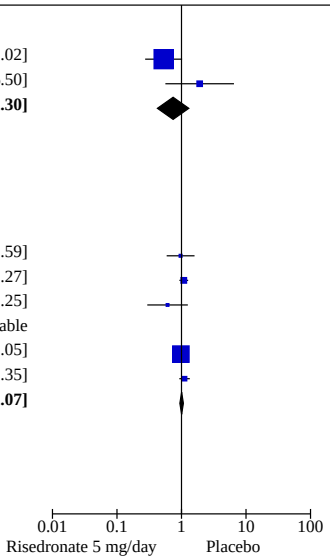




**Risk of bias legend**

(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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 7: Serious adverse events

| Study or Subgroup | Risedronate 5 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 |
|---|---|---|---|---|---|---|---|
| **1.7.1 Serious adverse events, Primary** | | | | | | | |
| Hooper 2005 | 12 | 129 | 22 | 125 | 84.6% | 0.53 [0.27 , 1.02] | + + + + - + + |
| Välimäki 2007 | 12 | 115 | 3 | 55 | 15.4% | 1.91 [0.56 , 6.50] | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **244** | | **180** | **100.0%** | **0.74 [0.42 , 1.30]** | |
| Total events: | 24 | | 25 | | | | |
| Heterogeneity: Chi² = 3.32, df = 1 (P = 0.07); I² = 70% | | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.29) | | | | | | | |
| **1.7.2 Serious adverse events, Secondary** | | | | | | | |
| Fogelman 2000 | 26 | 179 | 27 | 180 | 2.0% | 0.97 [0.59 , 1.59] | ? ? - - - + ? |
| Harris 1999 | 237 | 813 | 219 | 815 | 16.0% | 1.08 [0.93 , 1.27] | + + + + - + ? |
| Hosking 2003 | 15 | 222 | 12 | 108 | 1.2% | 0.61 [0.29 , 1.25] | + + + + - + + |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable | ? ? + + + + + |
| McClung 2001 | 943 | 3104 | 973 | 3134 | 70.9% | 0.98 [0.91 , 1.05] | ? ? + + - - + |
| Reginster 2000 | 151 | 408 | 135 | 407 | 9.9% | 1.12 [0.93 , 1.35] | ? ? - - - + ? |
| **Subtotal (95% CI)** | | **4757** | | **4678** | **100.0%** | **1.00 [0.94 , 1.07]** | |
| Total events: | 1372 | | 1366 | | | | |
| Heterogeneity: Chi² = 4.49, df = 4 (P = 0.34); I² = 11% | | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | | |

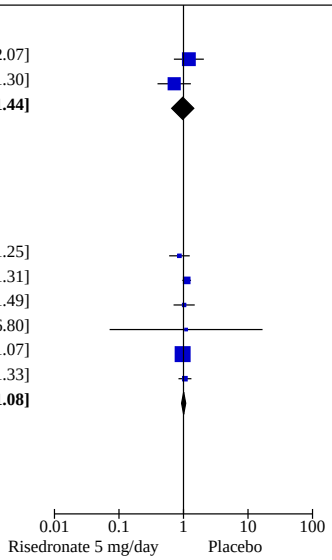



**Risk of bias legend**

(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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 8: Gastrointestinal adverse events

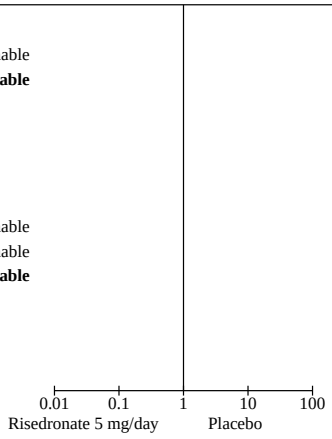
| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|
| **1.8.1 Gastrointestinal adverse events, Primary** | | | | | | | |
| Hooper 2005 | 25 | 129 | 20 | 125 | 51.7% | 1.21 [0.71 , 2.07] | + + + + - + + |
| Välimäki 2007 | 21 | 115 | 14 | 55 | 48.3% | 0.72 [0.40 , 1.30] | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **244** | | **180** | **100.0%** | **0.97 [0.66 , 1.44]** | |
| Total events: | 46 | | 34 | | | | |
| Heterogeneity: Chi² = 1.65, df = 1 (P = 0.20); I² = 40% | | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | | |
| **1.8.2 Gastrointestinal adverse events, Secondary** | | | | | | | |
| Fogelman 2000 | 40 | 177 | 47 | 180 | 4.3% | 0.87 [0.60 , 1.25] | ? ? - - - + ? |
| Harris 1999 | 245 | 813 | 219 | 815 | 20.1% | 1.12 [0.96 , 1.31] | + + + + - + ? |
| Hosking 2003 | 61 | 222 | 29 | 108 | 3.6% | 1.02 [0.70 , 1.49] | + + + + - + + |
| Leung 2005 | 1 | 31 | 1 | 34 | 0.1% | 1.10 [0.07 , 16.80] | ? ? + + + + + |
| McClung 2001 | 657 | 3104 | 684 | 3134 | 62.5% | 0.97 [0.88 , 1.07] | ? ? + + - - + |
| Reginster 2000 | 109 | 407 | 104 | 409 | 9.5% | 1.05 [0.84 , 1.33] | ? ? - - - + ? |
| **Subtotal (95% CI)** | | **4754** | | **4680** | **100.0%** | **1.01 [0.93 , 1.08]** | |
| Total events: | 1113 | | 1084 | | | | |
| Heterogeneity: Chi² = 3.29, df = 5 (P = 0.66); I² = 0% | | | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | | | |




**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: Risedronate 5 mg/day vs Placebo - Base case, Outcome 9: Atypical femoral fracture

| Study or Subgroup | Risedronate 5 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 |
|---|---|---|---|---|---|---|---|
| **1.9.1 Atypical femoral fracture, Primary** | | | | | | | |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable | ? ? + + ? + + |
| **Subtotal (95% CI)** | | **115** | | **55** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |
| **1.9.2 Atypical femoral fracture, Secondary** | | | | | | | |
| Harris 1999 | 0 | 669 | 0 | 660 | | Not estimable | + + + + - + ? |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable | ? ? + + + + + |
| **Subtotal (95% CI)** | | **697** | | **686** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |



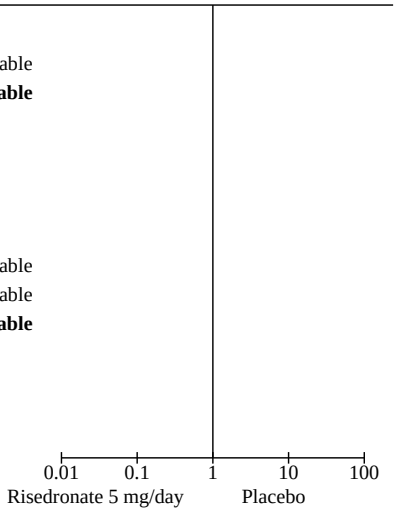

**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Safety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

**Comparison 2. Risedronate 5 mg/day vs Placebo - Subgroup of 1-year studies**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Clinical vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1.1 Clinical vertebral fractures, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.1.2 Clinical vertebral fractures, Secondary | 2 | 119 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.2 Non-vertebral Fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.2.1 Non-vertebral Fractures, Primary | 1 | 73 | Risk Ratio (M-H, Fixed, 95% CI) | 0.14 [0.01, 2.60] |
| 2.2.2 Non-vertebral Fractures, Secondary | 4 | 2559 | Risk Ratio (M-H, Fixed, 95% CI) | 0.76 [0.49, 1.20] |
| 2.3 Hip Fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.3.1 Hip Fractures, Primary | 2 | 243 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.3.2 Hip Fractures, Secondary | 2 | 119 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.4 Wrist Fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.4.1 Wrist Fractures, Primary | 1 | 73 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.4.2 Wrist Fractures, Secondary | 2 | 119 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.5 Radiographic vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.5.1 Radiographic vertebral fractures, Primary | 1 | 73 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.5.2 Radiographic vertebral fractures, Secondary | 2 | 1996 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.27, 0.59] |

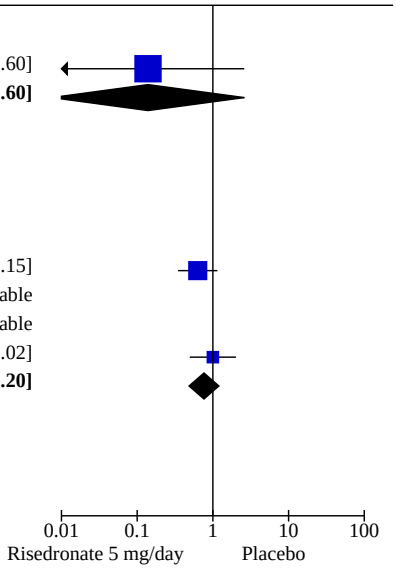
## Analysis 2.1. Comparison 2: Risedronate 5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 1: Clinical vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 Clinical vertebral fractures, Primary** | | | | | | |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable |
| **Subtotal (95% CI)** | | **115** | | **55** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **2.1.2 Clinical vertebral fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **59** | | **60** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



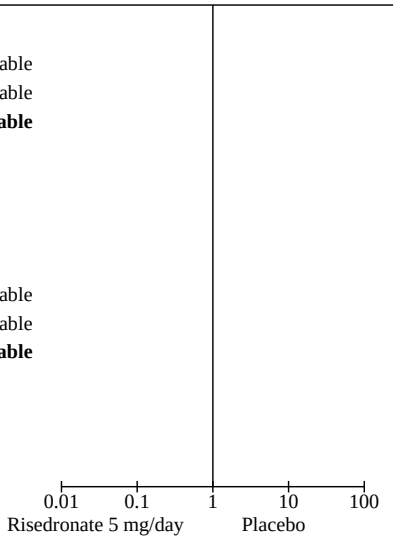

## Analysis 2.2. Comparison 2: Risedronate 5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 2: Non-vertebral Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.2.1 Non-vertebral Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 3 | 36 | 100.0% | 0.14 [0.01 , 2.60] |
| **Subtotal (95% CI)** | | **37** | | **36** | **100.0%** | **0.14 [0.01 , 2.60]** |
| Total events: | 0 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.32 (P = 0.19) | | | | | | |
| **2.2.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Harris 1999 | 17 | 813 | 27 | 815 | 64.3% | 0.63 [0.35 , 1.15] |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| Reginster 2000 | 15 | 406 | 15 | 406 | 35.7% | 1.00 [0.50 , 2.02] |
| **Subtotal (95% CI)** | | **1278** | | **1281** | **100.0%** | **0.76 [0.49 , 1.20]** |
| Total events: | 32 | | 42 | | | |
| Heterogeneity: $Chi^2 = 0.95$, df = 1 (P = 0.33); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | |



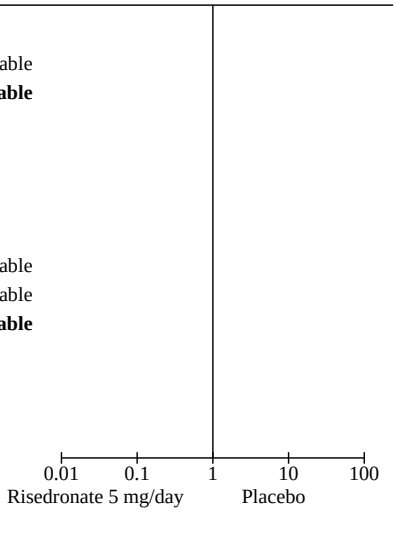
## Analysis 2.3. Comparison 2: Risedronate 5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 3: Hip Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.3.1 Hip Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable |
| **Subtotal (95% CI)** | | **152** | | **91** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **2.3.2 Hip Fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **59** | | **60** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |

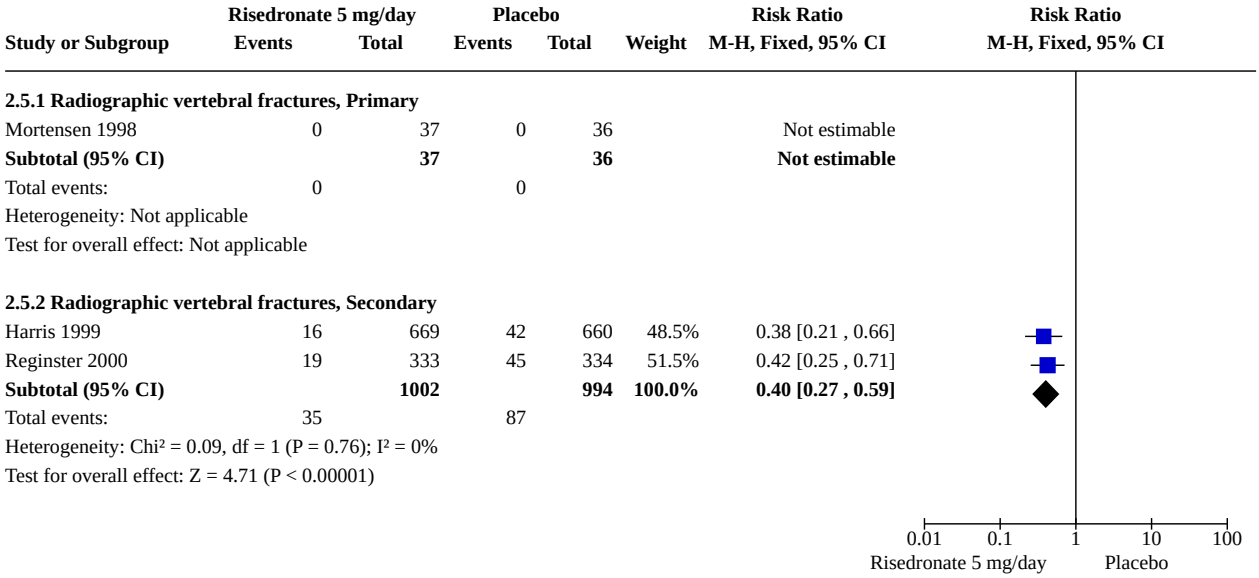



## Analysis 2.4. Comparison 2: Risedronate 5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 4: Wrist Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.4.1 Wrist Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| **Subtotal (95% CI)** | | **37** | | **36** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **2.4.2 Wrist Fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **59** | | **60** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



**Analysis 2.5. Comparison 2: Risedronate 5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 5: Radiographic vertebral fractures**

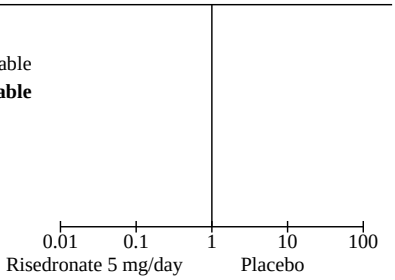



**Comparison 3. Risedronate 5 mg/day vs Placebo - Subgroup of 2-year studies**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Clinical vertebral fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1.1 Clinical vertebral Fractures, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 3.2 Non-vertebral Fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.2.1 Non-vertebral Fractures, Primary | 2 | 424 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.26, 1.90] |
| 3.2.2 Non-vertebral Fractures, Secondary | 3 | 2724 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.49, 0.91] |
| 3.3 Hip Fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.3.1 Hip Fractures, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 3.4 Wrist Fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.4.1 Wrist Fractures, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.03, 7.50] |
| 3.5 Radiographic vertebral fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.5.1 Radiographic vertebral fractures, Primary | 1 | 254 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.42, 2.25] |
| 3.5.2 Radiographic vertebral fractures, Secondary | 3 | 2152 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.36, 0.64] |

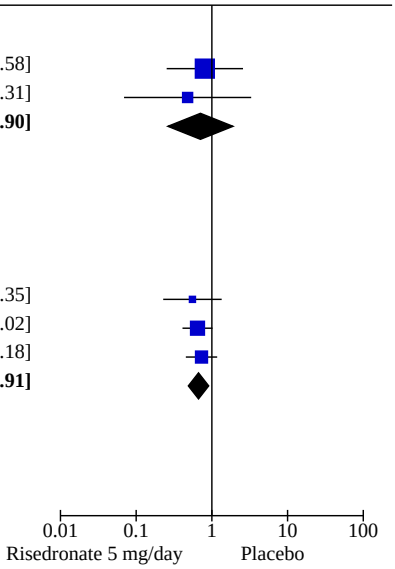
## Analysis 3.1. Comparison 3: Risedronate 5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 1: Clinical vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.1.1 Clinical vertebral Fractures, Primary** | | | | | | |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable |
| **Subtotal (95% CI)** | | **115** | | **55** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



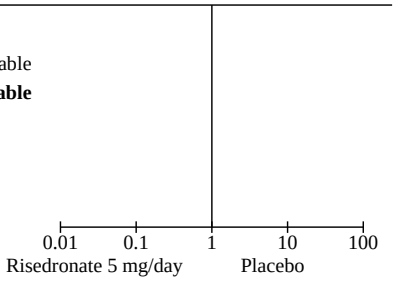

## Analysis 3.2. Comparison 3: Risedronate 5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 2: Non-vertebral Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.2.1 Non-vertebral Fractures, Primary** | | | | | | |
| Hooper 2005 | 5 | 129 | 6 | 125 | 69.3% | 0.81 [0.25 , 2.58] |
| Välimäki 2007 | 2 | 115 | 2 | 55 | 30.7% | 0.48 [0.07 , 3.31] |
| **Subtotal (95% CI)** | | **244** | | **180** | **100.0%** | **0.71 [0.26 , 1.90]** |
| Total events: | 7 | | 8 | | | |
| Heterogeneity: $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | | | |
| **3.2.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Fogelman 2000 | 7 | 140 | 13 | 144 | 13.5% | 0.55 [0.23 , 1.35] |
| Harris 1999 | 29 | 813 | 45 | 815 | 47.4% | 0.65 [0.41 , 1.02] |
| Reginster 2000 | 27 | 406 | 37 | 406 | 39.0% | 0.73 [0.45 , 1.18] |
| **Subtotal (95% CI)** | | **1359** | | **1365** | **100.0%** | **0.67 [0.49 , 0.91]** |
| Total events: | 63 | | 95 | | | |
| Heterogeneity: $Chi^2 = 0.32$, df = 2 (P = 0.85); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 2.58 (P = 0.010) | | | | | | |



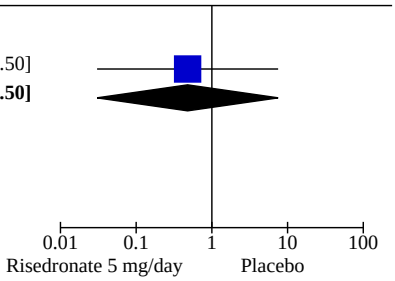
## Analysis 3.3. Comparison 3: Risedronate 5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 3: Hip Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.3.1 Hip Fractures, Primary** | | | | | | |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable |
| **Subtotal (95% CI)** | | **115** | | **55** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



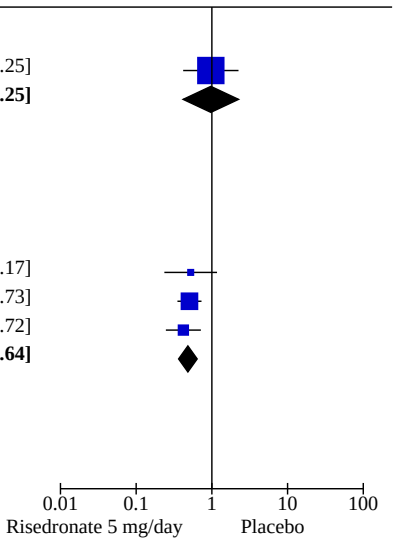

## Analysis 3.4. Comparison 3: Risedronate 5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 4: Wrist Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.4.1 Wrist Fractures, Primary** | | | | | | |
| Välimäki 2007 | 1 | 115 | 1 | 55 | 100.0% | 0.48 [0.03 , 7.50] |
| **Subtotal (95% CI)** | | **115** | | **55** | **100.0%** | **0.48 [0.03 , 7.50]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.53 (P = 0.60) | | | | | | |




## Analysis 3.5. Comparison 3: Risedronate 5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 5: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.5.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 10 | 129 | 10 | 125 | 100.0% | 0.97 [0.42 , 2.25] |
| **Subtotal (95% CI)** | | **129** | | **125** | **100.0%** | **0.97 [0.42 , 2.25]** |
| Total events: | 10 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.94) | | | | | | |
| **3.5.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 | 8 | 112 | 17 | 125 | 11.8% | 0.53 [0.24 , 1.17] |
| Harris 1999 | 40 | 669 | 78 | 660 | 57.8% | 0.51 [0.35 , 0.73] |
| Reginster 2000 | 18 | 303 | 40 | 283 | 30.4% | 0.42 [0.25 , 0.72] |
| **Subtotal (95% CI)** | | **1084** | | **1068** | **100.0%** | **0.48 [0.36 , 0.64]** |
| Total events: | 66 | | 135 | | | |
| Heterogeneity: $Chi^2 = 0.37$, df = 2 (P = 0.83); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 5.07 (P < 0.00001) | | | | | | |

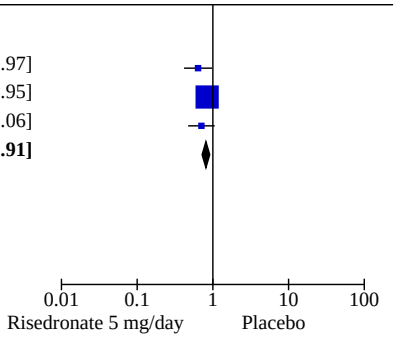


**Comparison 4. Risedronate 5 mg/day vs Placebo - Subgroup of 3-year studies**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Non-vertebral Fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.1.1 Non-vertebral Fractures, Secondary | 3 | 11770 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.72, 0.91] |
| 4.2 Hip Fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.2.1 Hip Fractures, Secondary | 1 | 9331 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.56, 0.94] |
| 4.3 Wrist Fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.3.1 Wrist Fractures, Secondary | 1 | 1627 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.33, 1.24] |
| 4.4 Radiographic vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.4.1 Radiographic vertebral fractures, Secondary | 2 | 2064 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.50, 0.77] |

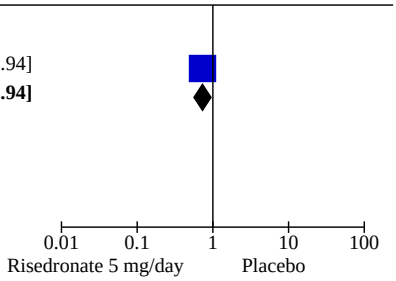
**Analysis 4.1. Comparison 4: Risedronate 5 mg/day vs Placebo - Subgroup of 3-year studies, Outcome 1: Non-vertebral Fractures**

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.1.1 Non-vertebral Fractures, Secondary** | | | | | | |
| Harris 1999 | 33 | 812 | 52 | 815 | 9.1% | 0.64 [0.42 , 0.97] |
| McClung 2001 | 583 | 6197 | 351 | 3134 | 81.9% | 0.84 [0.74 , 0.95] |
| Reginster 2000 | 36 | 406 | 51 | 406 | 9.0% | 0.71 [0.47 , 1.06] |
| **Subtotal (95% CI)** | | **7415** | | **4355** | **100.0%** | **0.81 [0.72 , 0.91]** |
| Total events: | 652 | | 454 | | | |
| Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.60 (P = 0.0003) | | | | | | |



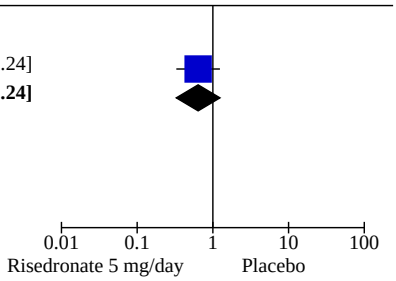
## Analysis 4.2. Comparison 4: Risedronate 5 mg/day vs Placebo - Subgroup of 3-year studies, Outcome 2: Hip Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.2.1 Hip Fractures, Secondary** | | | | | | |
| McClung 2001 | 137 | 6197 | 95 | 3134 | 100.0% | 0.73 [0.56 , 0.94] |
| **Subtotal (95% CI)** | | **6197** | | **3134** | **100.0%** | **0.73 [0.56 , 0.94]** |
| Total events: | 137 | | 95 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.40 (P = 0.02) | | | | | | |



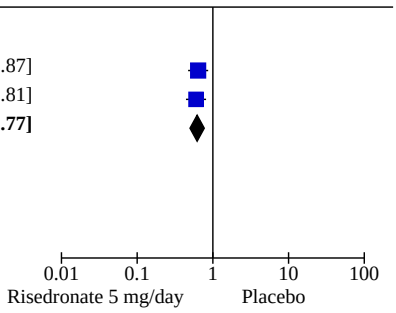

## Analysis 4.3. Comparison 4: Risedronate 5 mg/day vs Placebo - Subgroup of 3-year studies, Outcome 3: Wrist Fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.3.1 Wrist Fractures, Secondary** | | | | | | |
| Harris 1999 | 14 | 812 | 22 | 815 | 100.0% | 0.64 [0.33 , 1.24] |
| **Subtotal (95% CI)** | | **812** | | **815** | **100.0%** | **0.64 [0.33 , 1.24]** |
| Total events: | 14 | | 22 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.19) | | | | | | |




## Analysis 4.4. Comparison 4: Risedronate 5 mg/day vs Placebo - Subgroup of 3-year studies, Outcome 4: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.4.1 Radiographic vertebral fractures, Secondary** | | | | | | |
| Harris 1999 | 61 | 696 | 93 | 678 | 51.5% | 0.64 [0.47 , 0.87] |
| Reginster 2000 | 53 | 344 | 89 | 346 | 48.5% | 0.60 [0.44 , 0.81] |
| **Subtotal (95% CI)** | | **1040** | | **1024** | **100.0%** | **0.62 [0.50 , 0.77]** |
| Total events: | 114 | | 182 | | | |
| Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.77); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 4.34 (P < 0.0001) | | | | | | |

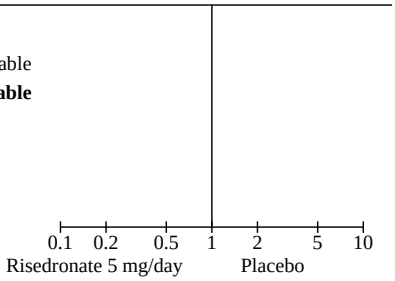


**Comparison 5. Risedronate 5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.1 Clinical vertebral fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.1.1 Clinical vertebral fractures, Secondary | 1 | 54 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 5.2 Non-vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.2.1 Non-vertebral Fractures, Primary | 1 | 254 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.25, 2.58] |
| 5.2.2 Non-vertebral Fractures, Secondary | 2 | 866 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.47, 1.06] |
| 5.3 Hip fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.3.1 Hip Fractures, Secondary | 1 | 54 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 5.4 Wrist fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.4.1 Wrist Fractures, Secondary | 1 | 54 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 5.5 Radiographic vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.5.1 Radiographic vertebral fractures, Primary | 1 | 254 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.42, 2.25] |
| 5.5.2 Radiographic vertebral fractures, Secondary | 1 | 690 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.44, 0.81] |

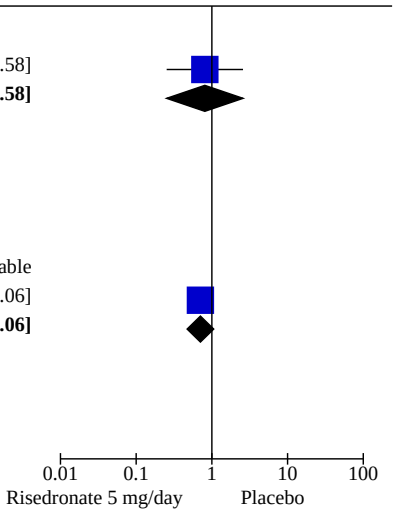
**Analysis 5.1. Comparison 5: Risedronate 5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 1: Clinical vertebral fractures**

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.1.1 Clinical vertebral fractures, Secondary** | | | | | | |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **28** | | **26** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



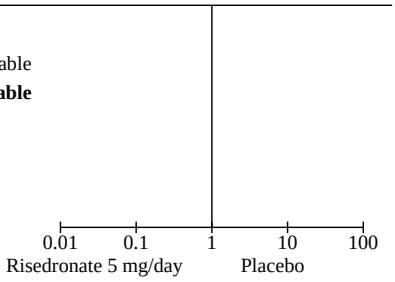
## Analysis 5.2. Comparison 5: Risedronate 5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 2: Non-vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.2.1 Non-vertebral Fractures, Primary** | | | | | | |
| Hooper 2005 | 5 | 129 | 6 | 125 | 100.0% | 0.81 [0.25 , 2.58] |
| **Subtotal (95% CI)** | | **129** | | **125** | **100.0%** | **0.81 [0.25 , 2.58]** |
| Total events: | 5 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | | |
| **5.2.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| Reginster 2000 | 36 | 406 | 51 | 406 | 100.0% | 0.71 [0.47 , 1.06] |
| **Subtotal (95% CI)** | | **434** | | **432** | **100.0%** | **0.71 [0.47 , 1.06]** |
| Total events: | 36 | | 51 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.69 (P = 0.09) | | | | | | |



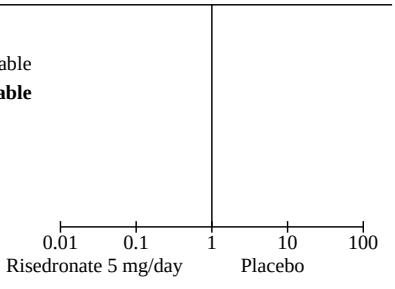

## Analysis 5.3. Comparison 5: Risedronate 5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 3: Hip fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.3.1 Hip Fractures, Secondary** | | | | | | |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **28** | | **26** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |

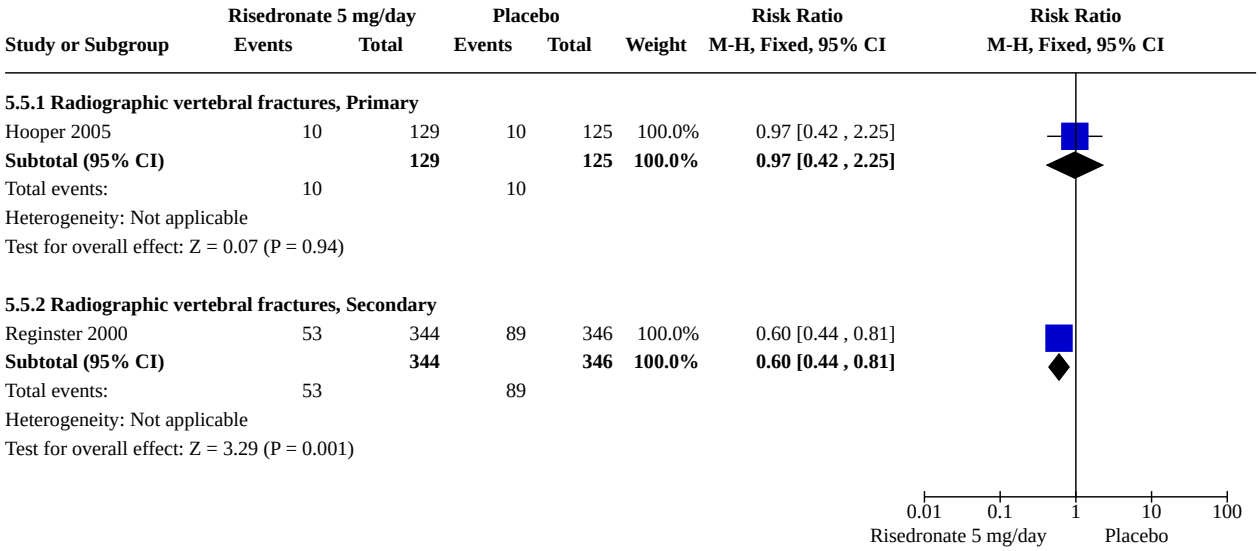



## Analysis 5.4. Comparison 5: Risedronate 5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 4: Wrist fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.4.1 Wrist Fractures, Secondary** | | | | | | |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **28** | | **26** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



### Analysis 5.5. Comparison 5: Risedronate 5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 5: Radiographic vertebral fractures



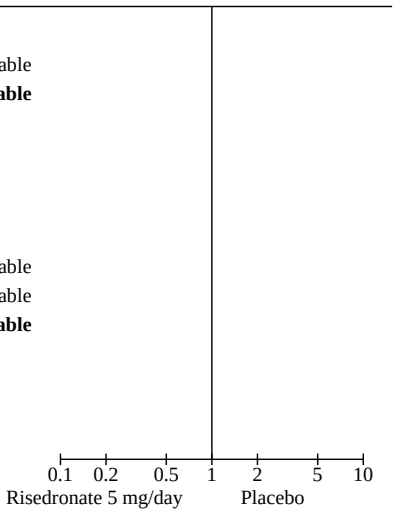

### Comparison 6. Risedronate 5 mg/day vs Placebo - Sensitivity analyses with baseline denominators

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.1 Clinical vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.1.1 Clinical vertebral fractures, Primary | 1 | 171 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 6.1.2 Clinical vertebral fractures, Secondary | 2 | 125 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 6.2 Non-vertebral fractures | 9 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.2.1 Non-vertebral Fractures, Primary | 3 | 499 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.22, 1.37] |
| 6.2.2 Non-vertebral Fractures, Secondary | 6 | 12272 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.72, 0.90] |
| 6.3 Hip fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.3.1 Hip Fractures, Primary | 2 | 244 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 6.3.2 Hip Fractures, Secondary | 3 | 9456 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.56, 0.94] |
| 6.4 Wrist fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.4.1 Wrist Fractures, Primary | 2 | 244 | Risk Ratio (M-H, Fixed, 95% CI) | 0.50 [0.03, 7.85] |
| 6.4.2 Wrist Fractures, Secondary | 3 | 1766 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.33, 1.23] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.5 Radiographic vertebral fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.5.1 Radiographic vertebral fractures, Primary | 2 | 328 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.42, 2.27] |
| 6.5.2 Radiographic vertebral fractures, Secondary | 3 | 2816 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.50, 0.76] |

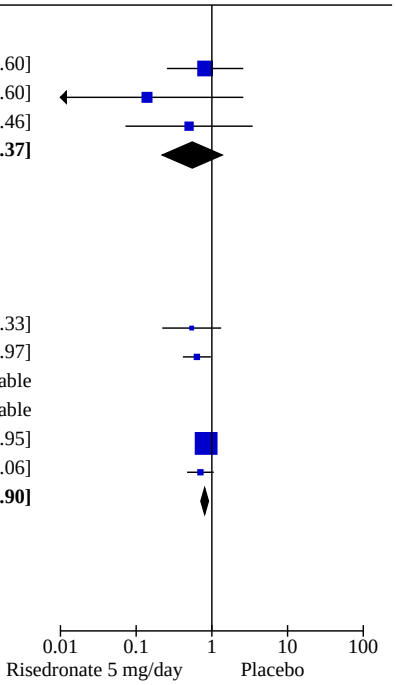
**Analysis 6.1. Comparison 6: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 1: Clinical vertebral fractures**

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.1.1 Clinical vertebral fractures, Primary** | | | | | | |
| Välimäki 2007 | 0 | 114 | 0 | 57 | | Not estimable |
| **Subtotal (95% CI)** | | **114** | | **57** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **6.1.2 Clinical vertebral fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 30 | 0 | 30 | | Not estimable |
| **Subtotal (95% CI)** | | **61** | | **64** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



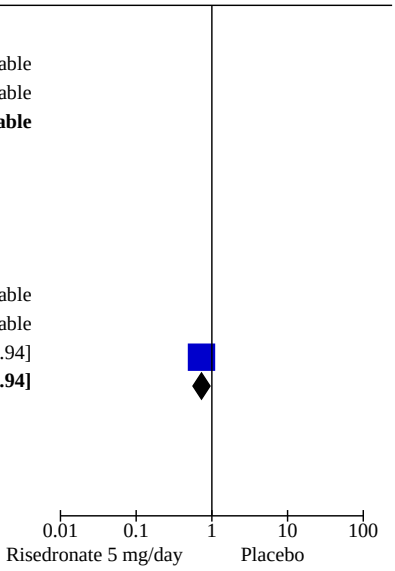
## Analysis 6.2. Comparison 6: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 2: Non-vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.2.1 Non-vertebral Fractures, Primary** | | | | | | |
| Hooper 2005 | 5 | 129 | 6 | 126 | 49.4% | 0.81 [0.25 , 2.60] |
| Mortensen 1998 | 0 | 37 | 3 | 36 | 28.9% | 0.14 [0.01 , 2.60] |
| Välimäki 2007 | 2 | 114 | 2 | 57 | 21.7% | 0.50 [0.07 , 3.46] |
| **Subtotal (95% CI)** | | **280** | | **219** | **100.0%** | **0.55 [0.22 , 1.37]** |
| Total events: | 7 | | 11 | | | |
| Heterogeneity: Chi² = 1.29, df = 2 (P = 0.52); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.28 (P = 0.20) | | | | | | |
| **6.2.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Fogelman 2000 | 7 | 179 | 13 | 180 | 2.2% | 0.54 [0.22 , 1.33] |
| Harris 1999 | 33 | 821 | 52 | 820 | 8.9% | 0.63 [0.41 , 0.97] |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 30 | 0 | 30 | | Not estimable |
| McClung 2001 | 583 | 6197 | 351 | 3134 | 80.1% | 0.84 [0.74 , 0.95] |
| Reginster 2000 | 36 | 408 | 51 | 408 | 8.8% | 0.71 [0.47 , 1.06] |
| **Subtotal (95% CI)** | | **7666** | | **4606** | **100.0%** | **0.80 [0.72 , 0.90]** |
| Total events: | 659 | | 467 | | | |
| Heterogeneity: Chi² = 2.82, df = 3 (P = 0.42); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.76 (P = 0.0002) | | | | | | |



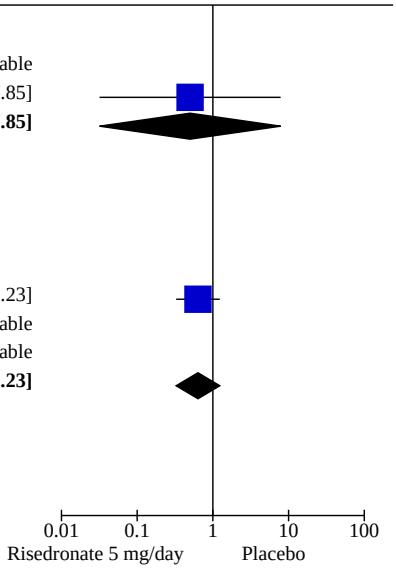

## Analysis 6.3. Comparison 6: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 3: Hip fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.3.1 Hip Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| Välimäki 2007 | 0 | 114 | 0 | 57 | | Not estimable |
| **Subtotal (95% CI)** | | **151** | | **93** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **6.3.2 Hip Fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 30 | 0 | 30 | | Not estimable |
| McClung 2001 | 137 | 6197 | 95 | 3134 | 100.0% | 0.73 [0.56 , 0.94] |
| **Subtotal (95% CI)** | | **6258** | | **3198** | **100.0%** | **0.73 [0.56 , 0.94]** |
| Total events: | 137 | | 95 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.40 (P = 0.02) | | | | | | |



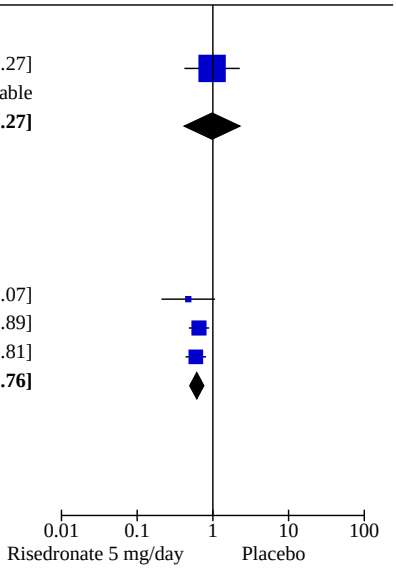
## Analysis 6.4. Comparison 6: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 4: Wrist fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.4.1 Wrist Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| Välimäki 2007 | 1 | 114 | 1 | 57 | 100.0% | 0.50 [0.03 , 7.85] |
| **Subtotal (95% CI)** | | **151** | | **93** | **100.0%** | **0.50 [0.03 , 7.85]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.49 (P = 0.62) | | | | | | |
| **6.4.2 Wrist Fractures, Secondary** | | | | | | |
| Harris 1999 | 14 | 821 | 22 | 820 | 100.0% | 0.64 [0.33 , 1.23] |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 30 | 0 | 30 | | Not estimable |
| **Subtotal (95% CI)** | | **882** | | **884** | **100.0%** | **0.64 [0.33 , 1.23]** |
| Total events: | 14 | | 22 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.34 (P = 0.18) | | | | | | |




## Analysis 6.5. Comparison 6: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 5: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.5.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 10 | 129 | 10 | 126 | 100.0% | 0.98 [0.42 , 2.27] |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| **Subtotal (95% CI)** | | **166** | | **162** | **100.0%** | **0.98 [0.42 , 2.27]** |
| Total events: | 10 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | | | |
| **6.5.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 | 8 | 179 | 17 | 180 | 8.5% | 0.47 [0.21 , 1.07] |
| Harris 1999 | 61 | 821 | 93 | 820 | 46.8% | 0.66 [0.48 , 0.89] |
| Reginster 2000 | 53 | 408 | 89 | 408 | 44.7% | 0.60 [0.44 , 0.81] |
| **Subtotal (95% CI)** | | **1408** | | **1408** | **100.0%** | **0.61 [0.50 , 0.76]** |
| Total events: | 122 | | 199 | | | |
| Heterogeneity: $Chi^2 = 0.60$, df = 2 (P = 0.74); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 4.54 (P < 0.00001) | | | | | | |

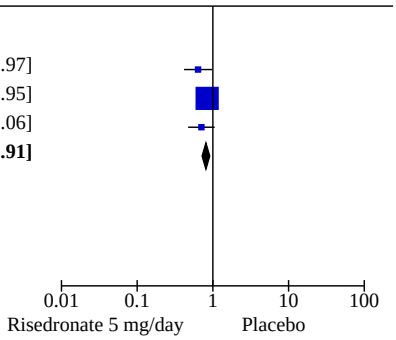


**Comparison 7. Risedronate 5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.1 Non-vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.1.1 Non-vertebral Fractures, Secondary | 3 | 11770 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.72, 0.91] |
| 7.2 Hip fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.2.1 Hip Fractures, Secondary | 1 | 9331 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.56, 0.94] |
| 7.3 Wrist fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.3.1 Wrist Fractures, Secondary | 1 | 1627 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.33, 1.24] |
| 7.4 Radiographic vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.4.1 Radiographic vertebral fractures, Secondary | 2 | 2064 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.50, 0.77] |

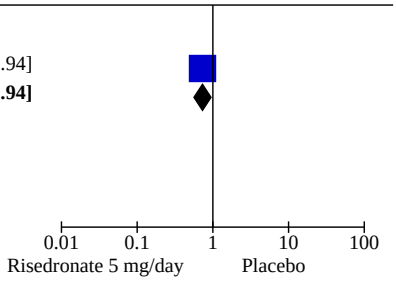
**Analysis 7.1. Comparison 7: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 1: Non-vertebral fractures**

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **7.1.1 Non-vertebral Fractures, Secondary** | | | | | | |
| Harris 1999 | 33 | 812 | 52 | 815 | 9.1% | 0.64 [0.42 , 0.97] |
| McClung 2001 | 583 | 6197 | 351 | 3134 | 81.9% | 0.84 [0.74 , 0.95] |
| Reginster 2000 | 36 | 406 | 51 | 406 | 9.0% | 0.71 [0.47 , 1.06] |
| **Subtotal (95% CI)** | | **7415** | | **4355** | **100.0%** | **0.81 [0.72 , 0.91]** |
| Total events: | 652 | | 454 | | | |
| Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.60 (P = 0.0003) | | | | | | |



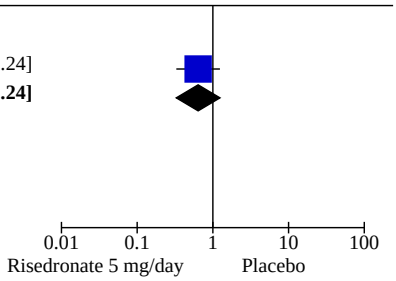
## Analysis 7.2. Comparison 7: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 2: Hip fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **7.2.1 Hip Fractures, Secondary** | | | | | | |
| McClung 2001 | 137 | 6197 | 95 | 3134 | 100.0% | 0.73 [0.56 , 0.94] |
| **Subtotal (95% CI)** | | **6197** | | **3134** | **100.0%** | **0.73 [0.56 , 0.94]** |
| Total events: | 137 | | 95 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.40 (P = 0.02) | | | | | | |



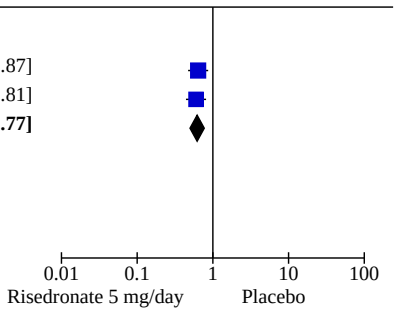

## Analysis 7.3. Comparison 7: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 3: Wrist fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **7.3.1 Wrist Fractures, Secondary** | | | | | | |
| Harris 1999 | 14 | 812 | 22 | 815 | 100.0% | 0.64 [0.33 , 1.24] |
| **Subtotal (95% CI)** | | **812** | | **815** | **100.0%** | **0.64 [0.33 , 1.24]** |
| Total events: | 14 | | 22 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.19) | | | | | | |




## Analysis 7.4. Comparison 7: Risedronate 5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 4: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **7.4.1 Radiographic vertebral fractures, Secondary** | | | | | | |
| Harris 1999 | 61 | 696 | 93 | 678 | 51.5% | 0.64 [0.47 , 0.87] |
| Reginster 2000 | 53 | 344 | 89 | 346 | 48.5% | 0.60 [0.44 , 0.81] |
| **Subtotal (95% CI)** | | **1040** | | **1024** | **100.0%** | **0.62 [0.50 , 0.77]** |
| Total events: | 114 | | 182 | | | |
| Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.77); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 4.34 (P < 0.0001) | | | | | | |

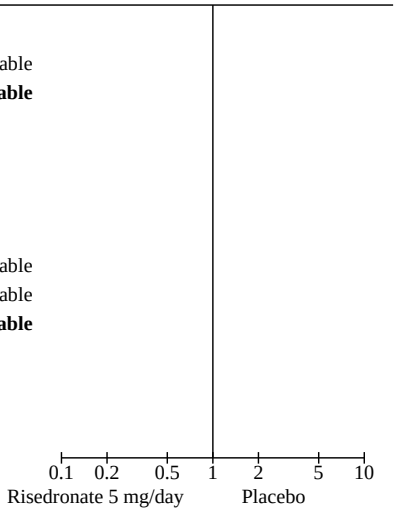


**Comparison 8. Risedronate 5 mg/day vs Placebo - Sensitivity analyses excluding McClung 2001 study**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.1 Clinical vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 8.1.1 Clinical vertebral fractures, Primary | 1 | 170 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8.1.2 Clinical vertebral fractures, Secondary | 2 | 119 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8.2 Non-vertebral fractures | 8 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 8.2.1 Non-vertebral Fractures, Primary | 3 | 497 | Risk Ratio (M-H, Fixed, 95% CI) | 0.54 [0.22, 1.35] |
| 8.2.2 Non-vertebral Fractures, Secondary | 5 | 2842 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.50, 0.87] |
| 8.3 Hip fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 8.3.1 Hip Fractures, Primary | 2 | 243 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8.3.2 Hip Fractures, Secondary | 2 | 119 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8.4 Wrist fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 8.4.1 Wrist Fractures, Primary | 2 | 243 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.03, 7.50] |
| 8.4.2 Wrist Fractures, Secondary | 3 | 1746 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.33, 1.24] |
| 8.5 Radiographic vertebral fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 8.5.1 Radiographic vertebral fractures, Primary | 2 | 327 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.42, 2.25] |
| 8.5.2 Radiographic vertebral fractures, Secondary | 3 | 2301 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.50, 0.75] |

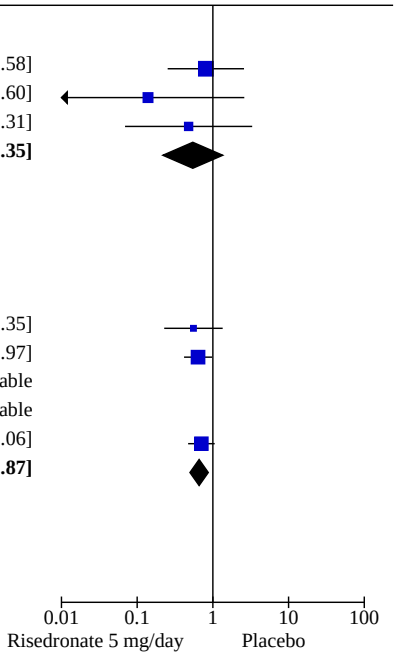
## Analysis 8.1. Comparison 8: Risedronate 5 mg/day vs Placebo - Sensitivity analyses excluding McClung 2001 study, Outcome 1: Clinical vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **8.1.1 Clinical vertebral fractures, Primary** | | | | | | |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable |
| **Subtotal (95% CI)** | | **115** | | **55** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **8.1.2 Clinical vertebral fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **59** | | **60** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |



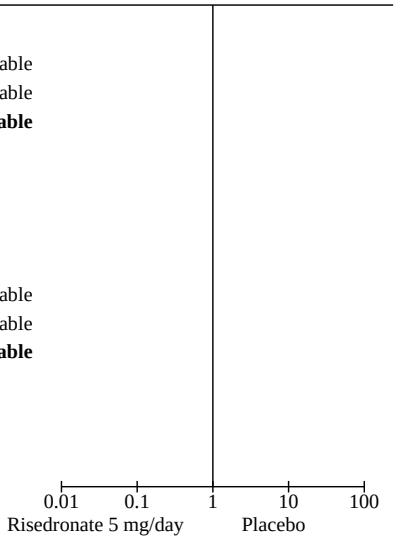

## Analysis 8.2. Comparison 8: Risedronate 5 mg/day vs Placebo - Sensitivity analyses excluding McClung 2001 study, Outcome 2: Non-vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **8.2.1 Non-vertebral Fractures, Primary** | | | | | | |
| Hooper 2005 | 5 | 129 | 6 | 125 | 49.4% | 0.81 [0.25 , 2.58] |
| Mortensen 1998 | 0 | 37 | 3 | 36 | 28.7% | 0.14 [0.01 , 2.60] |
| Välimäki 2007 | 2 | 115 | 2 | 55 | 21.9% | 0.48 [0.07 , 3.31] |
| **Subtotal (95% CI)** | | **281** | | **216** | **100.0%** | **0.54 [0.22 , 1.35]** |
| Total events: | 7 | | 11 | | | |
| Heterogeneity: $Chi^2 = 1.30$, df = 2 (P = 0.52); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.31 (P = 0.19) | | | | | | |
| **8.2.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Fogelman 2000 | 7 | 140 | 13 | 144 | 11.1% | 0.55 [0.23 , 1.35] |
| Harris 1999 | 33 | 812 | 52 | 815 | 44.9% | 0.64 [0.42 , 0.97] |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| Reginster 2000 | 36 | 406 | 51 | 406 | 44.1% | 0.71 [0.47 , 1.06] |
| **Subtotal (95% CI)** | | **1417** | | **1425** | **100.0%** | **0.66 [0.50 , 0.87]** |
| Total events: | 76 | | 116 | | | |
| Heterogeneity: $Chi^2 = 0.28$, df = 2 (P = 0.87); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 2.95 (P = 0.003) | | | | | | |



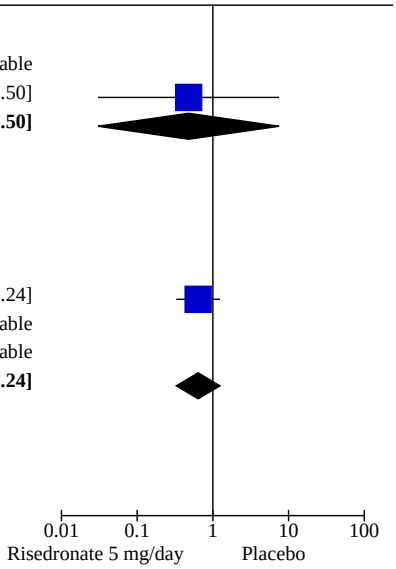
## Analysis 8.3. Comparison 8: Risedronate 5 mg/day vs Placebo - Sensitivity analyses excluding McClung 2001 study, Outcome 3: Hip fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **8.3.1 Hip Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| Välimäki 2007 | 0 | 115 | 0 | 55 | | Not estimable |
| **Subtotal (95% CI)** | | **152** | | **91** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **8.3.2 Hip Fractures, Secondary** | | | | | | |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **59** | | **60** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |

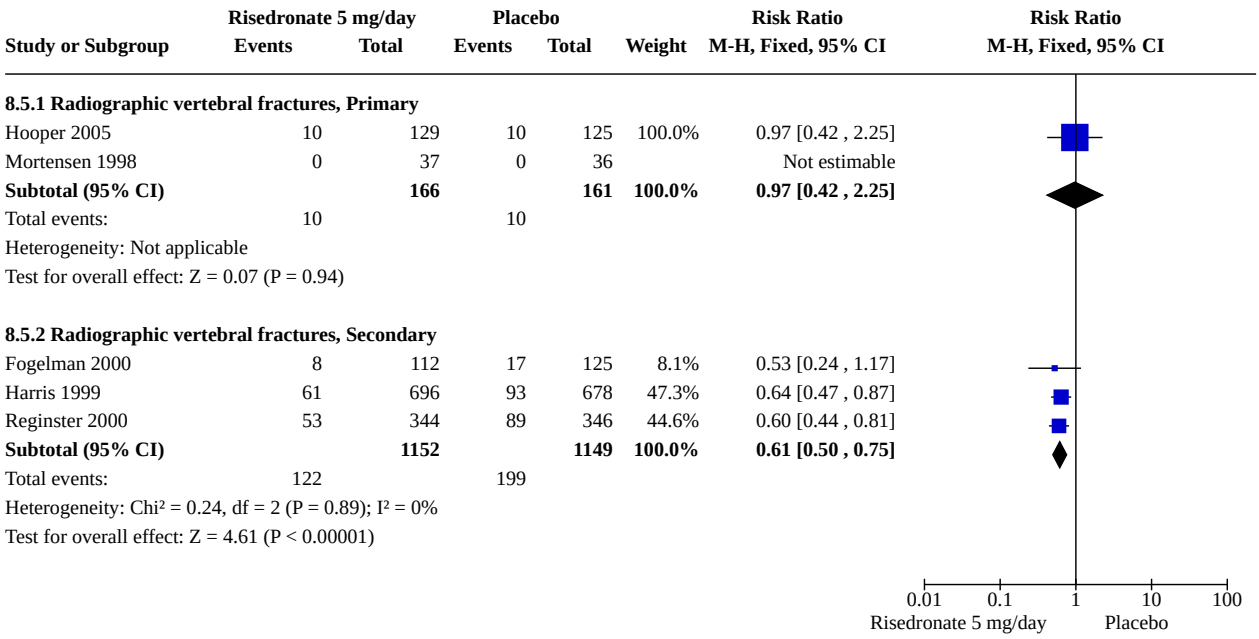



## Analysis 8.4. Comparison 8: Risedronate 5 mg/day vs Placebo - Sensitivity analyses excluding McClung 2001 study, Outcome 4: Wrist fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **8.4.1 Wrist Fractures, Primary** | | | | | | |
| Mortensen 1998 | 0 | 37 | 0 | 36 | | Not estimable |
| Välimäki 2007 | 1 | 115 | 1 | 55 | 100.0% | 0.48 [0.03 , 7.50] |
| **Subtotal (95% CI)** | | **152** | | **91** | **100.0%** | **0.48 [0.03 , 7.50]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.53 (P = 0.60) | | | | | | |
| **8.4.2 Wrist Fractures, Secondary** | | | | | | |
| Harris 1999 | 14 | 812 | 22 | 815 | 100.0% | 0.64 [0.33 , 1.24] |
| Leung 2005 | 0 | 31 | 0 | 34 | | Not estimable |
| Li 2005 | 0 | 28 | 0 | 26 | | Not estimable |
| **Subtotal (95% CI)** | | **871** | | **875** | **100.0%** | **0.64 [0.33 , 1.24]** |
| Total events: | 14 | | 22 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.19) | | | | | | |



### Analysis 8.5. Comparison 8: Risedronate 5 mg/day vs Placebo - Sensitivity analyses excluding McClung 2001 study, Outcome 5: Radiographic vertebral fractures



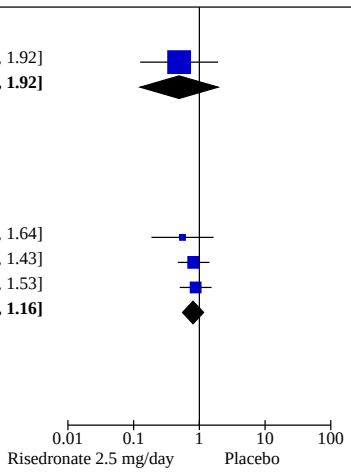

### Comparison 9. Risedronate 2.5 mg/day vs Placebo - Base case

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1 Non-vertebral fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.1.1 Non-vertebral fractures, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.13, 1.92] |
| 9.1.2 Non-vertebral fractures, Secondary | 3 | 2381 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.55, 1.16] |
| 9.2 Radiographic vertebral fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.2.1 Radiographic vertebral fractures, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.48, 2.46] |
| 9.2.2 Radiographic vertebral fractures, Secondary | 3 | 1994 | Risk Ratio (M-H, Fixed, 95% CI) | 0.63 [0.45, 0.87] |
| 9.3 Withdrawals due to adverse events | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.3.1 Withdrawals due to adverse events, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 1.48 [0.62, 3.49] |
| 9.3.2 Withdrawals due to adverse events, Secondary | 4 | 8710 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.81, 0.98] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.4 Serious adverse events | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.4.1 Serious adverse events, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 0.58 [0.31, 1.10] |
| 9.4.2 Serious adverse events, Secondary | 3 | 7084 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.91, 1.05] |
| 9.5 Gastrointestinal adverse events | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.5.1 Gastrointestinal adverse events, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 1.28 [0.75, 2.17] |
| 9.5.2 Gastrointestinal adverse events, Secondary | 2 | 7044 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.92, 1.10] |

## Analysis 9.1. Comparison 9: Risedronate 2.5 mg/day vs Placebo - Base case, Outcome 1: Non-vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A B C D E |
|---|---|---|---|---|---|---|---|
| **9.1.1 Non-vertebral fractures, Primary** | | | | | | | |
| Hooper 2005 | 3 | 127 | 6 | 125 | 100.0% | 0.49 [0.13 , 1.92] | + + + + + |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **0.49 [0.13 , 1.92]** | |
| Total events: | 3 | | 6 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | | |
| **9.1.2 Non-vertebral fractures, Secondary** | | | | | | | |
| Fogelman 2000 (1) | 4 | 80 | 13 | 144 | 15.3% | 0.55 [0.19 , 1.64] | ? ? - + ? |
| Harris 1999 | 22 | 811 | 27 | 815 | 44.5% | 0.82 [0.47 , 1.43] | + + + + ? |
| Reginster 2000 (2) | 20 | 248 | 26 | 283 | 40.1% | 0.88 [0.50 , 1.53] | ? ? - + ? |
| **Subtotal (95% CI)** | | **1139** | | **1242** | **100.0%** | **0.80 [0.55 , 1.16]** | |
| Total events: | 46 | | 66 | | | | |
| Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² = 0% | | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | | |




**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment at 9 of 13 centres. No further information about the mean duration of this group. Data were extracte

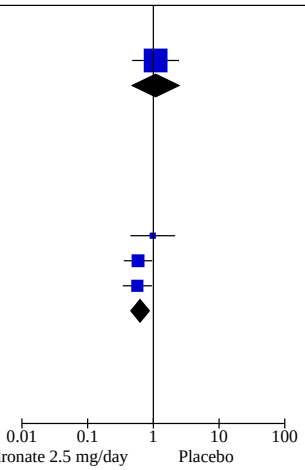
(2) The 2.5 mg/day group was discontinued by protocol amendment after 2 years, For "all years" data comparison related to risedronate 2.5 mg/day, data reported at year 1 were usec

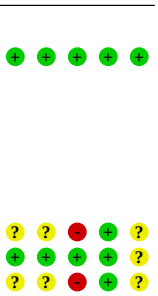
**Risk of bias legend**

(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: Risedronate 2.5 mg/day vs Placebo - Base case, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **9.2.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 11 | 127 | 10 | 125 | 100.0% | 1.08 [0.48 , 2.46] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **1.08 [0.48 , 2.46]** |
| Total events: | 11 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | | |
| **9.2.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 (1) | 8 | 60 | 17 | 125 | 12.4% | 0.98 [0.45 , 2.14] |
| Harris 1999 (2) | 23 | 618 | 42 | 660 | 45.6% | 0.58 [0.36 , 0.96] |
| Reginster 2000 (3) | 20 | 248 | 40 | 283 | 42.0% | 0.57 [0.34 , 0.95] |
| **Subtotal (95% CI)** | | **926** | | **1068** | **100.0%** | **0.63 [0.45 , 0.87]** |
| Total events: | 51 | | 99 | | | |
| Heterogeneity: Chi² = 1.46, df = 2 (P = 0.48); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.83 (P = 0.005) | | | | | | |




**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment at 9 of 13 centres. No further information about the mean duration of this group. Data were extracte

(2) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after the first year. For "all years" data comparison related to risedronate 2.5 mg/d, data reported at y

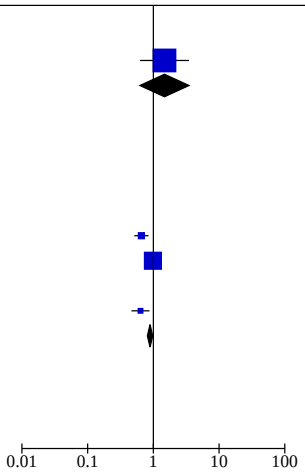
(3) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years. For "all years" data comparison related to risedronate 2.5 mg/day, data reported at yea

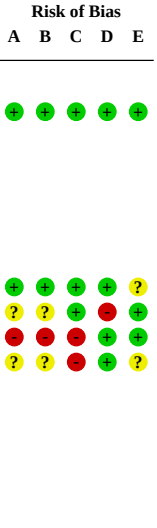
**Risk of bias legend**

(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: Risedronate 2.5 mg/day vs Placebo - Base case, Outcome 3: Withdrawals due to adverse events

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **9.3.1 Withdrawals due to adverse events, Primary** | | | | | | |
| Hooper 2005 | 12 | 127 | 8 | 125 | 100.0% | 1.48 [0.62 , 3.49] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **1.48 [0.62 , 3.49]** |
| Total events: | 12 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.89 (P = 0.37) | | | | | | |
| **9.3.2 Withdrawals due to adverse events, Secondary** | | | | | | |
| Harris 1999 (1) | 89 | 811 | 136 | 815 | 17.4% | 0.66 [0.51 , 0.84] |
| McClung 2001 | 548 | 3093 | 564 | 3134 | 71.9% | 0.98 [0.89 , 1.10] |
| Ohtori 2013 | 0 | 20 | 0 | 22 | | Not estimable |
| Reginster 2000 (2) | 53 | 408 | 83 | 407 | 10.7% | 0.64 [0.46 , 0.87] |
| **Subtotal (95% CI)** | | **4332** | | **4378** | **100.0%** | **0.89 [0.81 , 0.98]** |
| Total events: | 690 | | 783 | | | |
| Heterogeneity: Chi² = 13.42, df = 2 (P = 0.001); I² = 85% | | | | | | |
| Test for overall effect: Z = 2.44 (P = 0.01) | | | | | | |




**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after the first year. The incidences (after 1 year) were comparatively lower in 2.5 mg/day arm than tl

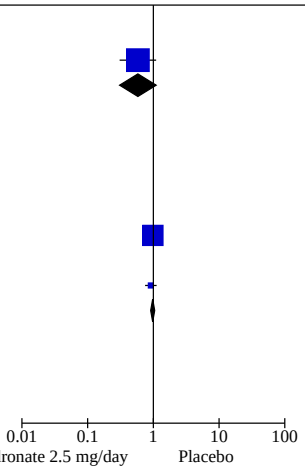
(2) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years of the 3-year study, from which 233 were withdrawn.

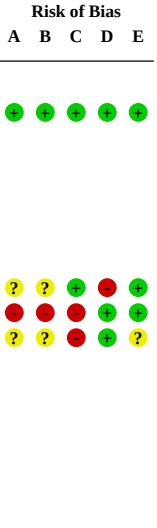
**Risk of bias legend**

(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: Risedronate 2.5 mg/day vs Placebo - Base case, Outcome 4: Serious adverse events

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **9.4.1 Serious adverse events, Primary** | | | | | | |
| Hooper 2005 | 13 | 127 | 22 | 125 | 100.0% | 0.58 [0.31 , 1.10] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **0.58 [0.31 , 1.10]** |
| Total events: | 13 | | 22 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.66 (P = 0.10) | | | | | | |
| **9.4.2 Serious adverse events, Secondary** | | | | | | |
| McClung 2001 | 946 | 3093 | 973 | 3134 | 87.7% | 0.99 [0.91 , 1.06] |
| Ohtori 2013 | 0 | 20 | 0 | 22 | | Not estimable |
| Reginster 2000 (1) | 124 | 408 | 135 | 407 | 12.3% | 0.92 [0.75 , 1.12] |
| **Subtotal (95% CI)** | | **3521** | | **3563** | **100.0%** | **0.98 [0.91 , 1.05]** |
| Total events: | 1070 | | 1108 | | | |
| Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |




**Footnotes**

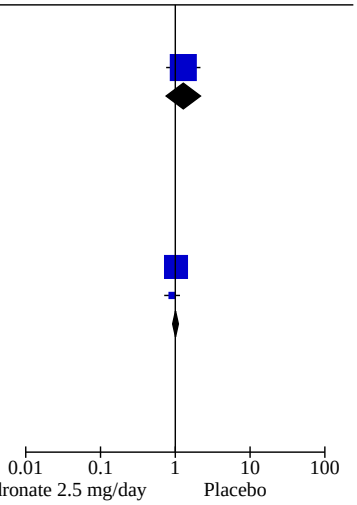
(1) Data were extracted as reported, although the 2.5 mg/day group was discontinued by protocol amendment after 2 years of the 3-year study.

**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: Risedronate 2.5 mg/day vs Placebo - Base case, Outcome 5: Gastrointestinal adverse events

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **9.5.1 Gastrointestinal adverse events, Primary** | | | | | | |
| Hooper 2005 | 26 | 127 | 20 | 125 | 100.0% | 1.28 [0.75 , 2.17] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **1.28 [0.75 , 2.17]** |
| Total events: | 26 | | 20 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.91 (P = 0.36) | | | | | | |
| **9.5.2 Gastrointestinal adverse events, Secondary** | | | | | | |
| McClung 2001 | 690 | 3093 | 684 | 3134 | 86.7% | 1.02 [0.93 , 1.12] |
| Reginster 2000 (1) | 94 | 408 | 104 | 409 | 13.3% | 0.91 [0.71 , 1.16] |
| **Subtotal (95% CI)** | | **3501** | | **3543** | **100.0%** | **1.01 [0.92 , 1.10]** |
| Total events: | 784 | | 788 | | | |
| Heterogeneity: Chi² = 0.82, df = 1 (P = 0.36); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | | |




**Footnotes**

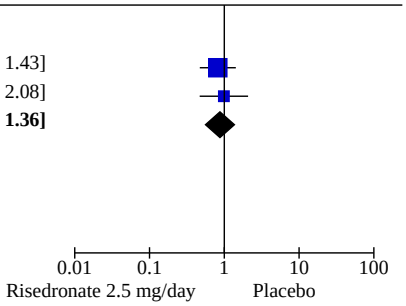
(1) Data were extracted as reported, although the 2.5 mg/day group was discontinued by protocol amendment after 2 years of the 3-year study.

## Comparison 10. Risedronate 2.5 mg/day vs Placebo - Subgroup of 1-year studies

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.1 Non-vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 10.1.1 Non-vertebral Fractures, Secondary | 2 | 2361 | Risk Ratio (M-H, Fixed, 95% CI) | 0.87 [0.56, 1.36] |
| 10.2 Radiographic vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 10.2.1 Radiographic vertebral fractures, Secondary | 2 | 1941 | Risk Ratio (M-H, Fixed, 95% CI) | 0.56 [0.40, 0.79] |

### Analysis 10.1. Comparison 10: Risedronate 2.5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 1: Non-vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **10.1.1 Non-vertebral Fractures, Secondary** | | | | | | |
| Harris 1999 | 22 | 811 | 27 | 815 | 66.7% | 0.82 [0.47 , 1.43] |
| Reginster 2000 (1) | 12 | 329 | 15 | 406 | 33.3% | 0.99 [0.47 , 2.08] |
| **Subtotal (95% CI)** | | **1140** | | **1221** | **100.0%** | **0.87 [0.56 , 1.36]** |
| Total events: | 34 | | 42 | | | |
| Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | | |

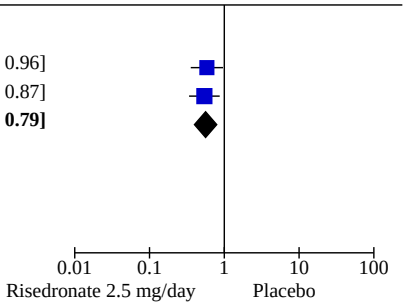



**Footnotes**

(1) The denominator of risedronate 2.5 mg/day arm was not reported but estimated by reducing the 1-year drop-out rate from the randomized at baseline.

### Analysis 10.2. Comparison 10: Risedronate 2.5 mg/day vs Placebo - Subgroup of 1-year studies, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **10.2.1 Radiographic vertebral fractures, Secondary** | | | | | | |
| Harris 1999 | 23 | 618 | 42 | 660 | 47.6% | 0.58 [0.36 , 0.96] |
| Reginster 2000 | 24 | 329 | 45 | 334 | 52.4% | 0.54 [0.34 , 0.87] |
| **Subtotal (95% CI)** | | **947** | | **994** | **100.0%** | **0.56 [0.40 , 0.79]** |
| Total events: | 47 | | 87 | | | |
| Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.30 (P = 0.0010) | | | | | | |



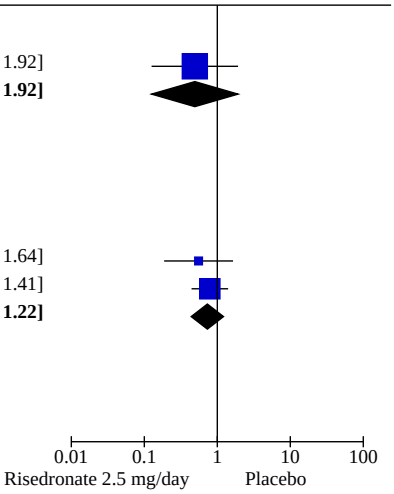

## Comparison 11. Risedronate 2.5 mg/day vs Placebo - Subgroup of 2-year studies

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 11.1 Non-vertebral Fractures | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 11.1.1 Non-vertebral Fractures, Primary | 1 | 252 | Risk Ratio (M-H, Random, 95% CI) | 0.49 [0.13, 1.92] |
| 11.1.2 Non-vertebral Fractures, Secondary | 2 | 755 | Risk Ratio (M-H, Random, 95% CI) | 0.73 [0.44, 1.22] |
| 11.2 Radiographic vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 11.2.1 Radiographic vertebral fractures, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.48, 2.46] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 11.2.2 Radiographic vertebral fractures, Secondary | 2 | 716 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.43, 1.01] |

## Analysis 11.1. Comparison 11: Risedronate 2.5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 1: Non-vertebral Fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **11.1.1 Non-vertebral Fractures, Primary** | | | | | | |
| Hooper 2005 | 3 | 127 | 6 | 125 | 100.0% | 0.49 [0.13 , 1.92] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **0.49 [0.13 , 1.92]** |
| Total events: | 3 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | |
| **11.1.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Fogelman 2000 (1) | 4 | 80 | 13 | 144 | 21.9% | 0.55 [0.19 , 1.64] |
| Reginster 2000 (2) | 18 | 248 | 26 | 283 | 78.1% | 0.79 [0.44 , 1.41] |
| **Subtotal (95% CI)** | | **328** | | **427** | **100.0%** | **0.73 [0.44 , 1.22]** |
| Total events: | 22 | | 39 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.21 (P = 0.23) | | | | | | |



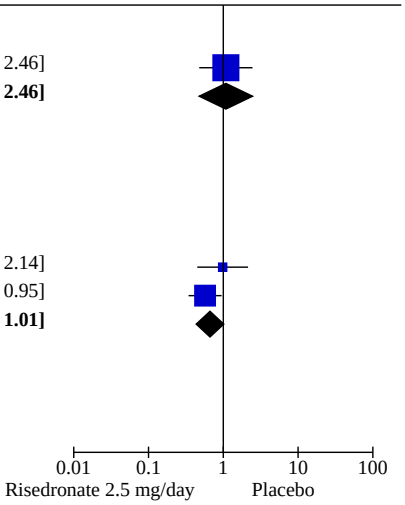

**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment at 9 of the 13 centers. No further information about the mean duration of this grou

(2) The denominators were not reported but estimated from the respective drop-out rates.

## Analysis 11.2. Comparison 11: Risedronate 2.5 mg/day vs Placebo - Subgroup of 2-year studies, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **11.2.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 11 | 127 | 10 | 125 | 100.0% | 1.08 [0.48 , 2.46] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **1.08 [0.48 , 2.46]** |
| Total events: | 11 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | | |
| **11.2.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 (1) | 8 | 60 | 17 | 125 | 22.8% | 0.98 [0.45 , 2.14] |
| Reginster 2000 (2) | 20 | 248 | 40 | 283 | 77.2% | 0.57 [0.34 , 0.95] |
| **Subtotal (95% CI)** | | **308** | | **408** | **100.0%** | **0.66 [0.43 , 1.01]** |
| Total events: | 28 | | 57 | | | |
| Heterogeneity: Chi² = 1.30, df = 1 (P = 0.26); I² = 23% | | | | | | |
| Test for overall effect: Z = 1.89 (P = 0.06) | | | | | | |




**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment at 9 of the 13 centres. No further information about the mean duration of this

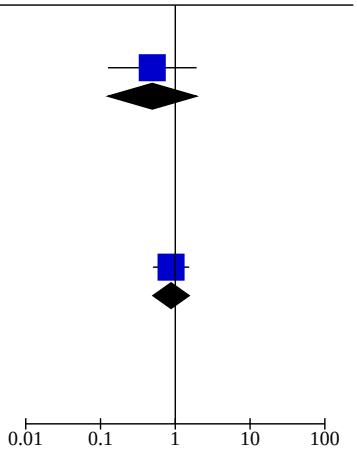
(2) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years. The denominators of 3 arms were not reported but estimated fro

## Comparison 12. Risedronate 2.5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 12.1 Non-vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 12.1.1 Non-vertebral fractures, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.13, 1.92] |
| 12.1.2 Non-vertebral fractures, Secondary | 1 | 531 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.50, 1.53] |
| 12.2 Radiographic vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 12.2.1 Radiographic vertebral fractures, Primary | 1 | 252 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.48, 2.46] |
| 12.2.2 Radiographic vertebral fractures, Secondary | 1 | 531 | Risk Ratio (M-H, Fixed, 95% CI) | 0.57 [0.34, 0.95] |

### Analysis 12.1. Comparison 12: Risedronate 2.5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 1: Non-vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **12.1.1 Non-vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 3 | 127 | 6 | 125 | 100.0% | 0.49 [0.13 , 1.92] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **0.49 [0.13 , 1.92]** |
| Total events: | 3 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | |
| **12.1.2 Non-vertebral fractures, Secondary** | | | | | | |
| Reginster 2000 (1) | 20 | 248 | 26 | 283 | 100.0% | 0.88 [0.50 , 1.53] |
| **Subtotal (95% CI)** | | **248** | | **283** | **100.0%** | **0.88 [0.50 , 1.53]** |
| Total events: | 20 | | 26 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.65) | | | | | | |

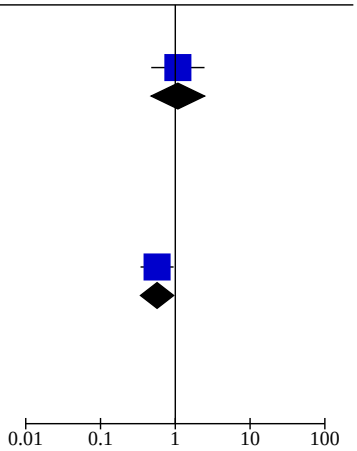



**Footnotes**

(1) The 2.5 mg/day group was discontinued by protocol amendment after 2 years. For "all years" data related to risedronate 2.5 mg/day, data reported at year 2

### Analysis 12.2. Comparison 12: Risedronate 2.5 mg/day vs Placebo - Subgroup of bisphosphonate-naive participants, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **12.2.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 11 | 127 | 10 | 125 | 100.0% | 1.08 [0.48 , 2.46] |
| **Subtotal (95% CI)** | | **127** | | **125** | **100.0%** | **1.08 [0.48 , 2.46]** |
| Total events: | 11 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | | |
| **12.2.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Reginster 2000 (1) | 20 | 248 | 40 | 283 | 100.0% | 0.57 [0.34 , 0.95] |
| **Subtotal (95% CI)** | | **248** | | **283** | **100.0%** | **0.57 [0.34 , 0.95]** |
| Total events: | 20 | | 40 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.16 (P = 0.03) | | | | | | |




**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years. For "all years" data comparison related to risedronate 2.5 mg/da

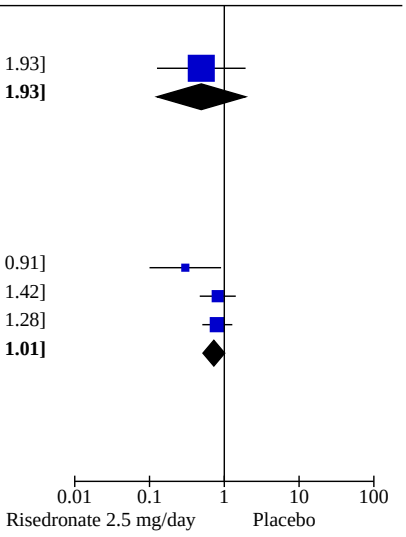
### Comparison 13. Risedronate 2.5 mg/day vs Placebo - Sensitivity analyses with baseline denominators

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 13.1 Non-vertebral Fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 13.1.1 Non-vertebral Fractures, Primary | 1 | 254 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.13, 1.93] |
| 13.1.2 Non-vertebral Fractures, Secondary | 3 | 2819 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.52, 1.01] |
| 13.2 Radiographic vertebral fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 13.2.1 Radiographic vertebral fractures, Primary | 1 | 254 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.48, 2.46] |
| 13.2.2 Radiographic vertebral fractures, Secondary | 3 | 2819 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.41, 0.74] |

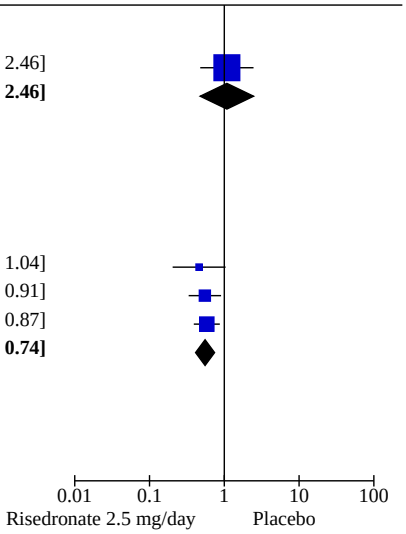
**Analysis 13.1. Comparison 13: Risedronate 2.5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 1: Non-vertebral Fractures**

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **13.1.1 Non-vertebral Fractures, Primary** | | | | | | |
| Hooper 2005 | 3 | 128 | 6 | 126 | 100.0% | 0.49 [0.13 , 1.93] |
| **Subtotal (95% CI)** | | **128** | | **126** | **100.0%** | **0.49 [0.13 , 1.93]** |
| Total events: | 3 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | |
| **13.1.2 Non-vertebral Fractures, Secondary** | | | | | | |
| Fogelman 2000 | 4 | 184 | 13 | 180 | 17.0% | 0.30 [0.10 , 0.91] |
| Harris 1999 | 22 | 817 | 27 | 820 | 34.9% | 0.82 [0.47 , 1.42] |
| Reginster 2000 | 30 | 410 | 37 | 408 | 48.1% | 0.81 [0.51 , 1.28] |
| **Subtotal (95% CI)** | | **1411** | | **1408** | **100.0%** | **0.72 [0.52 , 1.01]** |
| Total events: | 56 | | 77 | | | |
| Heterogeneity: $Chi^2 = 2.83$, df = 2 (P = 0.24); $I^2 = 29\%$ | | | | | | |
| Test for overall effect: Z = 1.89 (P = 0.06) | | | | | | |



### Analysis 13.2. Comparison 13: Risedronate 2.5 mg/day vs Placebo - Sensitivity analyses with baseline denominators, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **13.2.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 11 | 128 | 10 | 126 | 100.0% | 1.08 [0.48 , 2.46] |
| **Subtotal (95% CI)** | | **128** | | **126** | **100.0%** | **1.08 [0.48 , 2.46]** |
| Total events: | 11 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | | |
| **13.2.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 | 8 | 184 | 17 | 180 | 14.7% | 0.46 [0.20 , 1.04] |
| Harris 1999 | 23 | 817 | 42 | 820 | 35.8% | 0.55 [0.33 , 0.91] |
| Reginster 2000 | 34 | 410 | 58 | 408 | 49.6% | 0.58 [0.39 , 0.87] |
| **Subtotal (95% CI)** | | **1411** | | **1408** | **100.0%** | **0.55 [0.41 , 0.74]** |
| Total events: | 65 | | 117 | | | |
| Heterogeneity: $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 3.98 (P < 0.0001) | | | | | | |

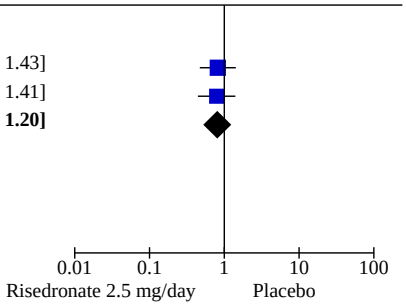



### Comparison 14. Risedronate 2.5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 14.1 Non-vertebral Fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 14.1.1 Non-vertebral Fractures, Secondary | 2 | 2157 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.54, 1.20] |
| 14.2 Radiographic vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 14.2.1 Radiographic vertebral fractures, Secondary | 2 | 1809 | Risk Ratio (M-H, Fixed, 95% CI) | 0.58 [0.41, 0.82] |

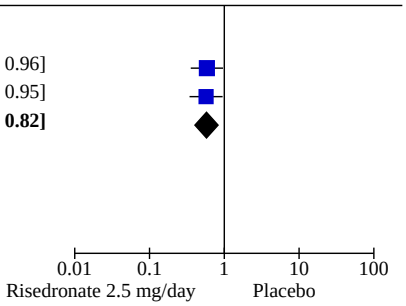
### Analysis 14.1. Comparison 14: Risedronate 2.5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 1: Non-vertebral Fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **14.1.1 Non-vertebral Fractures, Secondary** | | | | | | |
| Harris 1999 | 22 | 811 | 27 | 815 | 52.6% | 0.82 [0.47 , 1.43] |
| Reginster 2000 | 18 | 248 | 26 | 283 | 47.4% | 0.79 [0.44 , 1.41] |
| **Subtotal (95% CI)** | | **1059** | | **1098** | **100.0%** | **0.81 [0.54 , 1.20]** |
| Total events: | 40 | | 53 | | | |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.06 (P = 0.29) | | | | | | |




### Analysis 14.2. Comparison 14: Risedronate 2.5 mg/day vs Placebo - Sensitivity analyses with studies reporting fractures as efficacy outcomes, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 2.5 mg/day Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **14.2.1 Radiographic vertebral fractures, Secondary** | | | | | | |
| Harris 1999 | 23 | 618 | 42 | 660 | 52.1% | 0.58 [0.36 , 0.96] |
| Reginster 2000 | 20 | 248 | 40 | 283 | 47.9% | 0.57 [0.34 , 0.95] |
| **Subtotal (95% CI)** | | **866** | | **943** | **100.0%** | **0.58 [0.41 , 0.82]** |
| Total events: | 43 | | 82 | | | |
| Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.02 (P = 0.003) | | | | | | |



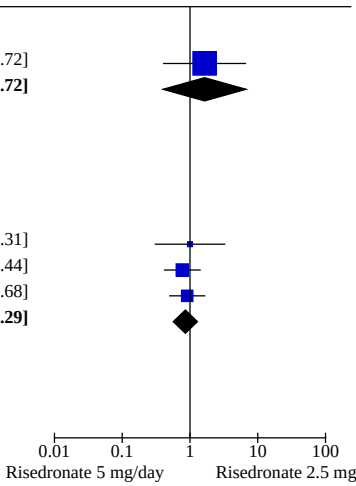

### Comparison 15. Risedronate 5 mg/day vs Risedronate 2.5 mg/day

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 15.1 Non-vertebral fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.1.1 Non-vertebral fractures, Primary | 1 | 256 | Risk Ratio (M-H, Fixed, 95% CI) | 1.64 [0.40, 6.72] |
| 15.1.2 Non-vertebral fractures, Secondary | 3 | 2395 | Risk Ratio (M-H, Fixed, 95% CI) | 0.85 [0.57, 1.29] |
| 15.2 Radiographic vertebral fractures | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.2.1 Radiographic vertebral fractures, Primary | 1 | 256 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.39, 2.03] |
| 15.2.2 Radiographic vertebral fractures, Secondary | 3 | 2010 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.44, 0.98] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 15.3 Withdrawals due to adverse events | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.3.1 Withdrawals due to adverse events, Primary | 1 | 256 | Risk Ratio (M-H, Fixed, 95% CI) | 0.57 [0.23, 1.41] |
| 15.3.2 Withdrawals due to adverse events, Secondary | 3 | 8636 | Risk Ratio (M-H, Fixed, 95% CI) | 1.09 [0.99, 1.20] |
| 15.4 Serious adverse events | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.4.1 Serious adverse events, Primary | 1 | 256 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.43, 1.91] |
| 15.4.2 Serious adverse events, Secondary | 2 | 7013 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.95, 1.09] |
| 15.5 Gastrointestinal adverse events | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.5.1 Gastrointestinal adverse events, Primary | 1 | 256 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.58, 1.55] |
| 15.5.2 Gastrointestinal adverse events, Secondary | 2 | 7013 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.89, 1.06] |

## Analysis 15.1. Comparison 15: Risedronate 5 mg/day vs Risedronate 2.5 mg/day, Outcome 1: Non-vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Risedronate 5 mg/day Total | Risedronate 2.5 mg/day Events | Risedronate 2.5 mg/day Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **15.1.1 Non-vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 5 | 129 | 3 | 127 | 100.0% | 1.64 [0.40 , 6.72] |
| **Subtotal (95% CI)** | | **129** | | **127** | **100.0%** | **1.64 [0.40 , 6.72]** |
| Total events: | 5 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | | | |
| **15.1.2 Non-vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 (1) | 7 | 140 | 4 | 80 | 10.9% | 1.00 [0.30 , 3.31] |
| Harris 1999 | 17 | 813 | 22 | 811 | 47.0% | 0.77 [0.41 , 1.44] |
| Reginster 2000 (2) | 20 | 303 | 18 | 248 | 42.2% | 0.91 [0.49 , 1.68] |
| **Subtotal (95% CI)** | | **1256** | | **1139** | **100.0%** | **0.85 [0.57 , 1.29]** |
| Total events: | 44 | | 44 | | | |
| Heterogeneity: Chi² = 0.21, df = 2 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | | | |



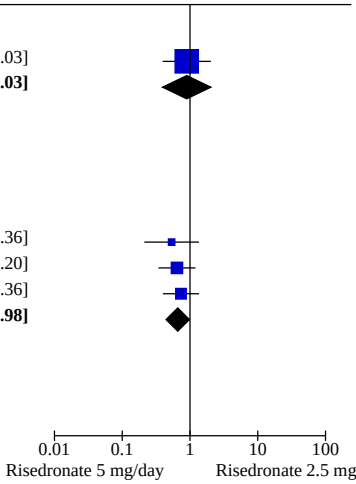

**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment at 9 of 13 centres. No further information about the mean duration of this group. Data were ext

(2) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years, For "all years" data related to risedronate 2.5 mg/day, data reported at year 2 was

## Analysis 15.2. Comparison 15: Risedronate 5 mg/day vs Risedronate 2.5 mg/day, Outcome 2: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate 2.5 mg/day Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **15.2.1 Radiographic vertebral fractures, Primary** | | | | | | |
| Hooper 2005 | 10 | 129 | 11 | 127 | 100.0% | 0.89 [0.39 , 2.03] |
| **Subtotal (95% CI)** | | **129** | | **127** | **100.0%** | **0.89 [0.39 , 2.03]** |
| Total events: | 10 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.79) | | | | | | |
| **15.2.2 Radiographic vertebral fractures, Secondary** | | | | | | |
| Fogelman 2000 (1) | 8 | 112 | 8 | 60 | 18.5% | 0.54 [0.21 , 1.36] |
| Harris 1999 (2) | 16 | 669 | 23 | 618 | 42.5% | 0.64 [0.34 , 1.20] |
| Reginster 2000 (3) | 18 | 303 | 20 | 248 | 39.1% | 0.74 [0.40 , 1.36] |
| **Subtotal (95% CI)** | | **1084** | | **926** | **100.0%** | **0.66 [0.44 , 0.98]** |
| Total events: | 42 | | 51 | | | |
| Heterogeneity: Chi² = 0.32, df = 2 (P = 0.85); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.05 (P = 0.04) | | | | | | |

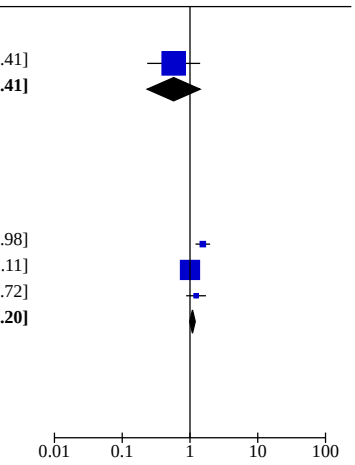



**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment at 9 out of 13 centres. No further information about the mean duration of this group. Data was
(2) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after the first year. For "all years" comparison related to risedronate 2.5 mg/day, data reported
(3) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years, For "all years" comparison related to risedronate 2.5 mg/day, data reported at yea

## Analysis 15.3. Comparison 15: Risedronate 5 mg/day vs Risedronate 2.5 mg/day, Outcome 3: Withdrawals due to adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate 2.5 mg/day Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **15.3.1 Withdrawals due to adverse events, Primary** | | | | | | |
| Hooper 2005 | 7 | 129 | 12 | 127 | 100.0% | 0.57 [0.23 , 1.41] |
| **Subtotal (95% CI)** | | **129** | | **127** | **100.0%** | **0.57 [0.23 , 1.41]** |
| Total events: | 7 | | 12 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.21 (P = 0.23) | | | | | | |
| **15.3.2 Withdrawals due to adverse events, Secondary** | | | | | | |
| Harris 1999 (1) | 138 | 813 | 89 | 811 | 12.9% | 1.55 [1.21 , 1.98] |
| McClung 2001 | 550 | 3104 | 548 | 3093 | 79.4% | 1.00 [0.90 , 1.11] |
| Reginster 2000 (2) | 65 | 407 | 53 | 408 | 7.7% | 1.23 [0.88 , 1.72] |
| **Subtotal (95% CI)** | | **4324** | | **4312** | **100.0%** | **1.09 [0.99 , 1.20]** |
| Total events: | 753 | | 690 | | | |
| Heterogeneity: Chi² = 10.60, df = 2 (P = 0.005); I² = 81% | | | | | | |
| Test for overall effect: Z = 1.76 (P = 0.08) | | | | | | |

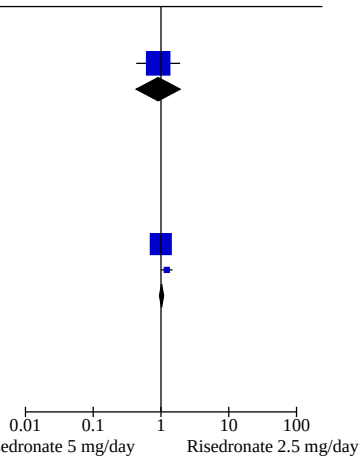



**Footnotes**

(1) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after the first year. For "all years" comparison related to risedronate 2.5 mg/day, data reported
(2) The arm of risedronate 2.5 mg/day was discontinued by protocol amendment after 2 years of the 3-year study, from which 233 were withdrawn.

## Analysis 15.4. Comparison 15: Risedronate 5 mg/day vs Risedronate 2.5 mg/day, Outcome 4: Serious adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate 2.5 mg/day Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **15.4.1 Serious adverse events, Primary** | | | | | | |
| Hooper 2005 | 12 | 129 | 13 | 127 | 100.0% | 0.91 [0.43 , 1.91] |
| **Subtotal (95% CI)** | | **129** | | **127** | **100.0%** | **0.91 [0.43 , 1.91]** |
| Total events: | 12 | | 13 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.25 (P = 0.80) | | | | | | |
| **15.4.2 Serious adverse events, Secondary** | | | | | | |
| McClung 2001 | 943 | 3104 | 946 | 3093 | 88.4% | 0.99 [0.92 , 1.07] |
| Reginster 2000 (1) | 151 | 408 | 124 | 408 | 11.6% | 1.22 [1.00 , 1.48] |
| **Subtotal (95% CI)** | | **3512** | | **3501** | **100.0%** | **1.02 [0.95 , 1.09]** |
| Total events: | 1094 | | 1070 | | | |
| Heterogeneity: Chi² = 3.69, df = 1 (P = 0.05); I² = 73% | | | | | | |
| Test for overall effect: Z = 0.53 (P = 0.59) | | | | | | |

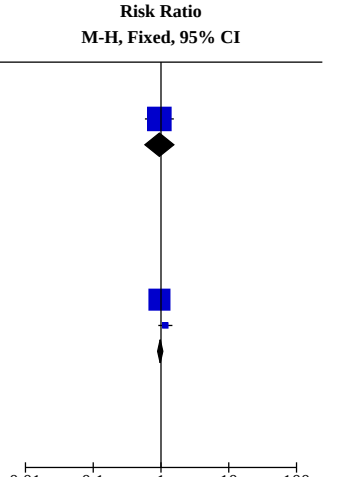



**Footnotes**

(1) Data were extracted as reported, although the 2.5 mg/day group was discontinued by protocol amendment after 2 years of the 3-year study.

## Analysis 15.5. Comparison 15: Risedronate 5 mg/day vs Risedronate 2.5 mg/day, Outcome 5: Gastrointestinal adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate 2.5 mg/day Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **15.5.1 Gastrointestinal adverse events, Primary** | | | | | | |
| Hooper 2005 | 25 | 129 | 26 | 127 | 100.0% | 0.95 [0.58 , 1.55] |
| **Subtotal (95% CI)** | | **129** | | **127** | **100.0%** | **0.95 [0.58 , 1.55]** |
| Total events: | 25 | | 26 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.22 (P = 0.83) | | | | | | |
| **15.5.2 Gastrointestinal adverse events, Secondary** | | | | | | |
| McClung 2001 | 657 | 3104 | 690 | 3093 | 88.0% | 0.95 [0.86 , 1.04] |
| Reginster 2000 (1) | 109 | 408 | 94 | 408 | 12.0% | 1.16 [0.91 , 1.47] |
| **Subtotal (95% CI)** | | **3512** | | **3501** | **100.0%** | **0.97 [0.89 , 1.06]** |
| Total events: | 766 | | 784 | | | |
| Heterogeneity: Chi² = 2.34, df = 1 (P = 0.13); I² = 57% | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | | |




**Footnotes**

(1) Data was extracted as reported, although the 2.5 mg/day group was discontinued by protocol amendment after 2 years of the 3-year study.

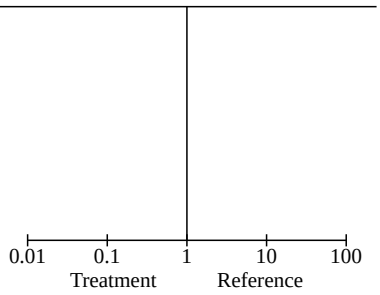
## Comparison 16. Risedronate vs Active comparators- Clinical vertebral fractures

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 16.1 Treatment vs Reference, Primary | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 16.1.1 Risedronate 5 mg/day vs Raloxifene 60 mg/day | 1 | 200 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 16.2 Treatment vs Reference, Secondary | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 16.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 3 | 392 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 16.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 2 | 180 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 16.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | 0.33 [0.01, 8.16] |

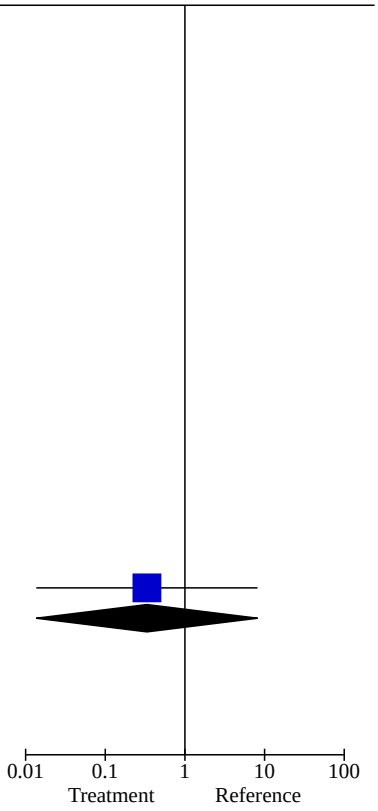
**Analysis 16.1. Comparison 16: Risedronate vs Active comparators-Clinical vertebral fractures, Outcome 1: Treatment vs Reference, Primary**

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **16.1.1 Risedronate 5 mg/day vs Raloxifene 60 mg/day** | | | | | | |
| Muscoso 2004 | 0 | 100 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **100** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



### Analysis 16.2. Comparison 16: Risedronate vs Active comparators- Clinical vertebral fractures, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **16.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Akyol 2006 | 0 | 52 | 0 | 60 | | Not estimable |
| Galesanu 2011 | 0 | 32 | 0 | 133 | | Not estimable |
| Paggiosi 2014a | 0 | 58 | 0 | 57 | | Not estimable |
| **Subtotal (95% CI)** | | **142** | | **250** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **16.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month** | | | | | | |
| Galesanu 2011 | 0 | 32 | 0 | 33 | | Not estimable |
| Paggiosi 2014a | 0 | 58 | 0 | 57 | | Not estimable |
| **Subtotal (95% CI)** | | **90** | | **90** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **16.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC** | | | | | | |
| Roux 2014 | 0 | 429 | 1 | 429 | 100.0% | 0.33 [0.01 , 8.16] |
| **Subtotal (95% CI)** | | **429** | | **429** | **100.0%** | **0.33 [0.01 , 8.16]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.50) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



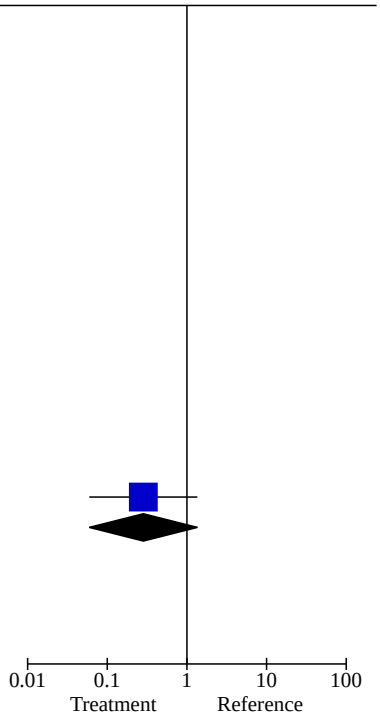

### Comparison 17. Risedronate vs Active comparators- Non-vertebral fractures

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 17.1 Treatment vs Reference, Primary | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 17.1.1 Risedronate 5 mg/day vs Clodronate 100 mg/week, IM | 1 | 900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 17.1.2 Risedronate 5 mg/day vs Raloxifene 60 mg/day | 1 | 200 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 17.1.3 (Risedronate 5 mg/day + HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | 0.28 [0.06, 1.35] |
| 17.2 Treatment vs Reference, Secondary | 7 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 17.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 3 | 327 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 17.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 1 | 65 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 17.2.3 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 2 | 2070 | Risk Ratio (M-H, Fixed, 95% CI) | 1.28 [0.90, 1.82] |
| 17.2.4 Risedronate 2.5 mg/day vs Etidronate 200 mg/day | 1 | 235 | Risk Ratio (M-H, Fixed, 95% CI) | 1.74 [0.52, 5.77] |
| 17.2.5 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 1 | 1874 | Risk Ratio (M-H, Fixed, 95% CI) | 1.18 [0.66, 2.13] |

**Analysis 17.1. Comparison 17: Risedronate vs Active comparators-Non-vertebral fractures, Outcome 1: Treatment vs Reference, Primary**

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **17.1.1 Risedronate 5 mg/day vs Clodronate 100 mg/week, IM** | | | | | | |
| Muscoso 2004 | 0 | 100 | 0 | 800 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **800** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **17.1.2 Risedronate 5 mg/day vs Raloxifene 60 mg/day** | | | | | | |
| Muscoso 2004 | 0 | 100 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **100** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **17.1.3 (Risedronate 5 mg/day + HRT) vs HRT** | | | | | | |
| Harris 2001 (1) | 2 | 263 | 7 | 261 | 100.0% | 0.28 [0.06 , 1.35] |
| **Subtotal (95% CI)** | | **263** | | **261** | **100.0%** | **0.28 [0.06 , 1.35]** |
| Total events: | 2 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.58 (P = 0.11) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

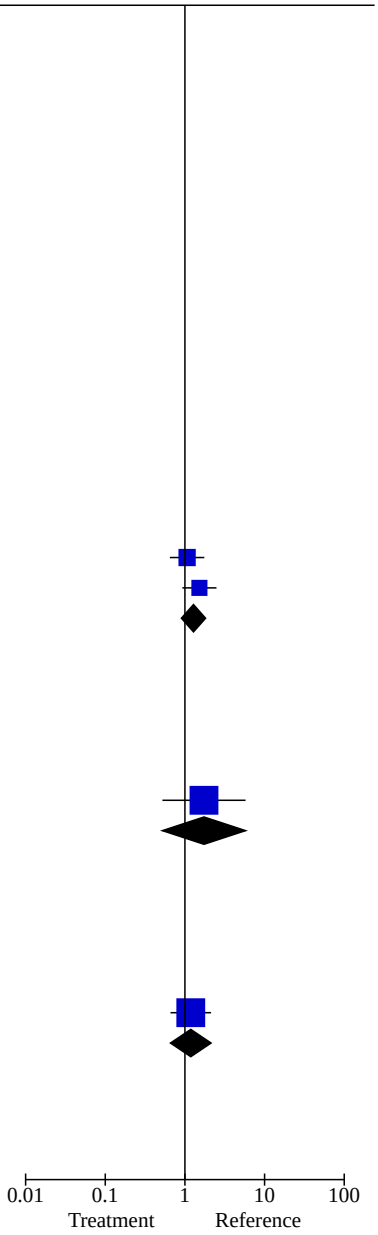



**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 17.2. Comparison 17: Risedronate vs Active comparators- Non-vertebral fractures, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **17.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Akyol 2006 | 0 | 52 | 0 | 60 | | Not estimable |
| Galesanu 2011 | 0 | 32 | 0 | 133 | | Not estimable |
| Sarioglu 2006 (1) | 0 | 25 | 0 | 25 | | Not estimable |
| **Subtotal (95% CI)** | | **109** | | **218** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **17.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month** | | | | | | |
| Galesanu 2011 | 0 | 32 | 0 | 33 | | Not estimable |
| **Subtotal (95% CI)** | | **32** | | **33** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **17.2.3 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Hadji 2012 | 29 | 350 | 28 | 360 | 52.5% | 1.07 [0.65 , 1.75] |
| Kendler 2018 | 38 | 680 | 25 | 680 | 47.5% | 1.52 [0.93 , 2.49] |
| **Subtotal (95% CI)** | | **1030** | | **1040** | **100.0%** | **1.28 [0.90 , 1.82]** |
| Total events: | 67 | | 53 | | | |
| Heterogeneity: $Chi^2 = 0.99$, df = 1 (P = 0.32); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.39 (P = 0.16) | | | | | | |
| **17.2.4 Risedronate 2.5 mg/day vs Etidronate 200 mg/day** | | | | | | |
| Fukunaga 2002 | 7 | 118 | 4 | 117 | 100.0% | 1.74 [0.52 , 5.77] |
| **Subtotal (95% CI)** | | **118** | | **117** | **100.0%** | **1.74 [0.52 , 5.77]** |
| Total events: | 7 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.90 (P = 0.37) | | | | | | |
| **17.2.5 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day)** | | | | | | |
| Tanaka 2017 (2) | 24 | 943 | 20 | 931 | 100.0% | 1.18 [0.66 , 2.13] |
| **Subtotal (95% CI)** | | **943** | | **931** | **100.0%** | **1.18 [0.66 , 2.13]** |
| Total events: | 24 | | 20 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.31$, df = 2 (P = 0.86), $I^2 = 0\%$ | | | | | | |




**Footnotes**

(1) Risedonate 5 mg/day was compared with alendronate 70 mg/week.

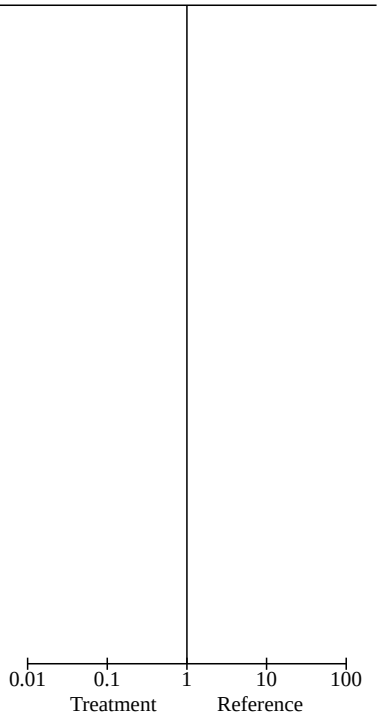
(2) Risedronate was provided daily at 2.5 mg or weekly at 17.5 mg.

**Comparison 18. Risedronate vs Active comparators- Hip fractures**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 18.1 Treatment vs Reference, Primary | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 18.1.1 Risedronate 5 mg/day vs Clodronate 100 mg/week, IM | 1 | 900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 18.1.2 Risedronate 5 mg/day vs Raloxifene 60 mg/day | 1 | 200 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 18.1.3 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 18.2 Treatment vs Reference, Secondary | 8 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 18.2.1 Risedronate 5 mg/day or 35 mg/week vs Alendronate 70 mg/day | 4 | 442 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 18.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 2 | 180 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 18.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.06, 15.94] |
| 18.2.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 2 | 2070 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.36, 2.89] |
| 18.2.5 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 1 | 1874 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

## Analysis 18.1. Comparison 18: Risedronate vs Active comparators- Hip fractures, Outcome 1: Treatment vs Reference, Primary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **18.1.1 Risedronate 5 mg/day vs Clodronate 100 mg/week, IM** | | | | | | |
| Muscoso 2004 (1) | 0 | 100 | 0 | 800 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **800** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **18.1.2 Risedronate 5 mg/day vs Raloxifene 60 mg/day** | | | | | | |
| Muscoso 2004 | 0 | 100 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **100** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **18.1.3 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | |
| Harris 2001 (2) | 0 | 263 | 0 | 261 | | Not estimable |
| **Subtotal (95% CI)** | | **263** | | **261** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



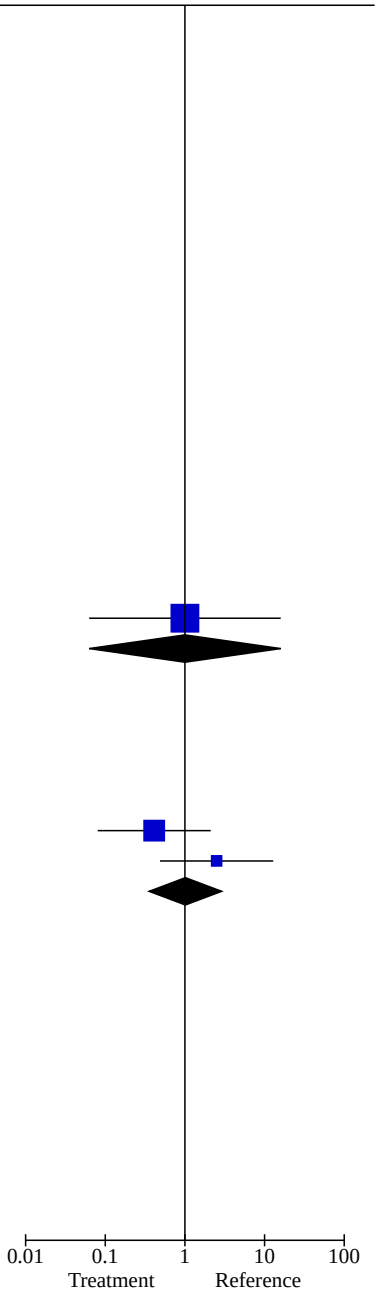

**Footnotes**

(1) The attrition was not reported, so the numbers of the randomized participants were used for denominators.

(2) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 18.2. Comparison 18: Risedronate vs Active comparators- Hip fractures, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **18.2.1 Risedronate 5 mg/day or 35 mg/week vs Alendronate 70 mg/day** | | | | | | |
| Akyol 2006 | 0 | 52 | 0 | 60 | | Not estimable |
| Galesanu 2011 | 0 | 32 | 0 | 133 | | Not estimable |
| Paggiosi 2014a | 0 | 58 | 0 | 57 | | Not estimable |
| Sarioglu 2006 (1) | 0 | 25 | 0 | 25 | | Not estimable |
| **Subtotal (95% CI)** | | **167** | | **275** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **18.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month** | | | | | | |
| Galesanu 2011 | 0 | 32 | 0 | 33 | | Not estimable |
| Paggiosi 2014a | 0 | 58 | 0 | 57 | | Not estimable |
| **Subtotal (95% CI)** | | **90** | | **90** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **18.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC** | | | | | | |
| Roux 2014 | 1 | 429 | 1 | 429 | 100.0% | 1.00 [0.06 , 15.94] |
| **Subtotal (95% CI)** | | **429** | | **429** | **100.0%** | **1.00 [0.06 , 15.94]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | |
| **18.2.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Hadji 2012 | 2 | 350 | 5 | 360 | 71.1% | 0.41 [0.08 , 2.11] |
| Kendler 2018 | 5 | 680 | 2 | 680 | 28.9% | 2.50 [0.49 , 12.84] |
| **Subtotal (95% CI)** | | **1030** | | **1040** | **100.0%** | **1.01 [0.36 , 2.89]** |
| Total events: | 7 | | 7 | | | |
| Heterogeneity: Chi² = 2.34, df = 1 (P = 0.13); I² = 57% | | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.98) | | | | | | |
| **18.2.5 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day)** | | | | | | |
| Tanaka 2017 (2) | 0 | 943 | 0 | 931 | | Not estimable |
| **Subtotal (95% CI)** | | **943** | | **931** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0% | | | | | | |




**Footnotes**

(1) Risedonate 5 mg/day compared with alendronate 70 mg/week.

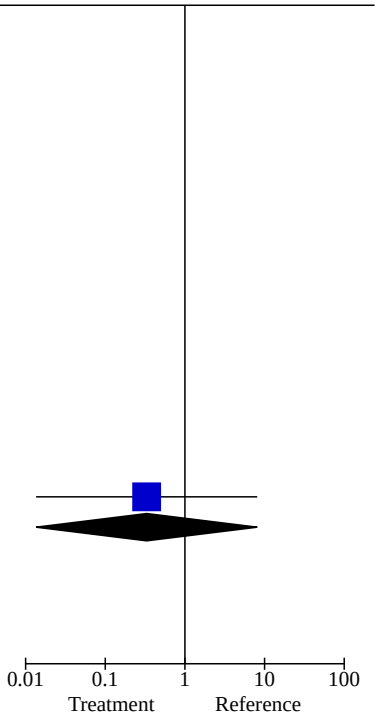
(2) Risedronate 2.5 mg/d or 17.5 mg/wk was used in two arms

**Comparison 19. Risedronate vs Active comparators- Wrist fractures**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 19.1 Treatment vs Reference, Primary | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 19.1.1 Risedronate 5 mg/day vs Clodronate 100 mg/week, IM | 1 | 900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 19.1.2 Risedronate 5 mg/day vs Raloxifene 60 mg/day | 1 | 200 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 19.1.3 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | 0.33 [0.01, 8.08] |
| 19.2 Treatment vs Reference, Secondary | 6 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 19.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 3 | 327 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 19.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 1 | 65 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 19.2.3 Risedronate 5 mg/day vs Teriparatide 20 µg/day, SC | 2 | 2076 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.15, 2.56] |
| 19.2.4 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 1 | 1874 | Risk Ratio (M-H, Fixed, 95% CI) | 0.33 [0.01, 8.07] |

## Analysis 19.1. Comparison 19: Risedronate vs Active comparators- Wrist fractures, Outcome 1: Treatment vs Reference, Primary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **19.1.1 Risedronate 5 mg/day vs Clodronate 100 mg/week, IM** | | | | | | |
| Muscoso 2004 | 0 | 100 | 0 | 800 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **800** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **19.1.2 Risedronate 5 mg/day vs Raloxifene 60 mg/day** | | | | | | |
| Muscoso 2004 | 0 | 100 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **100** | | **100** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **19.1.3 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | |
| Harris 2001 (1) | 0 | 263 | 1 | 261 | 100.0% | 0.33 [0.01 , 8.08] |
| **Subtotal (95% CI)** | | **263** | | **261** | **100.0%** | **0.33 [0.01 , 8.08]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

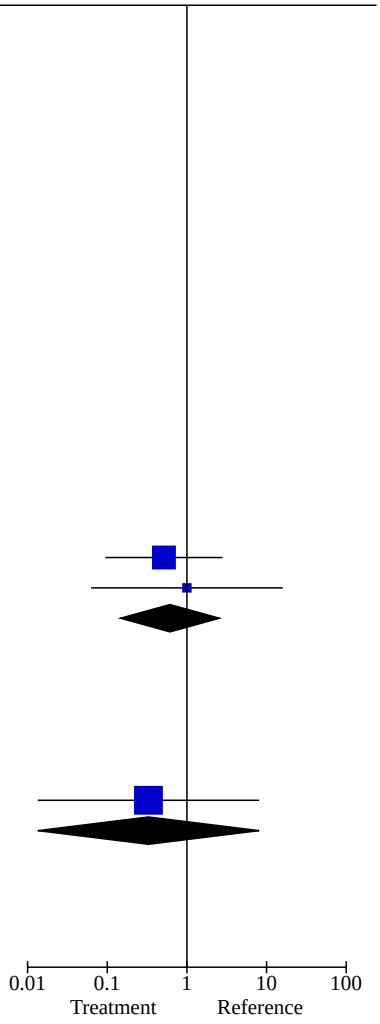



**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 19.2. Comparison 19: Risedronate vs Active comparators- Wrist fractures, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **19.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Akyol 2006 | 0 | 52 | 0 | 60 | | Not estimable |
| Galesanu 2011 | 0 | 32 | 0 | 133 | | Not estimable |
| Sarioglu 2006 (1) | 0 | 25 | 0 | 25 | | Not estimable |
| **Subtotal (95% CI)** | | **109** | | **218** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **19.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month** | | | | | | |
| Galesanu 2011 | 0 | 32 | 0 | 33 | | Not estimable |
| **Subtotal (95% CI)** | | **32** | | **33** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **19.2.3 Risedronate 5 mg/day vs Teriparatide 20 µg/day, SC** | | | | | | |
| Hadji 2012 | 2 | 350 | 4 | 360 | 79.8% | 0.51 [0.09 , 2.79] |
| Kendler 2018 | 1 | 683 | 1 | 683 | 20.2% | 1.00 [0.06 , 15.96] |
| **Subtotal (95% CI)** | | **1033** | | **1043** | **100.0%** | **0.61 [0.15 , 2.56]** |
| Total events: | 3 | | 5 | | | |
| Heterogeneity: $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.50) | | | | | | |
| **19.2.4 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day)** | | | | | | |
| Tanaka 2017 (2) | 0 | 943 | 1 | 931 | 100.0% | 0.33 [0.01 , 8.07] |
| **Subtotal (95% CI)** | | **943** | | **931** | **100.0%** | **0.33 [0.01 , 8.07]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.12$, df = 1 (P = 0.73), $I^2 = 0\%$ | | | | | | |




**Footnotes**

(1) Risedonate 5 mg/day was compared with alendronate 70 mg/week.

(2) Risedronate 2.5 mg/d or 17.5 mg/wk was used in two arms.

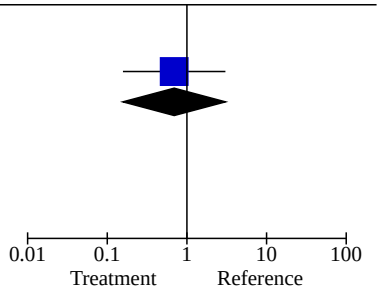
## Comparison 20. Risedronate vs Active comparators- Radiographic vertebral fractures

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 20.1 Treatment vs Reference, Primary | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 20.1.1 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 323 | Risk Ratio (M-H, Fixed, 95% CI) | 0.69 [0.16, 3.04] |
| 20.2 Treatment vs Reference, Secondary | 7 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 20.2.1 Risedronate 5 mg/day vs Alendronate 70 mg/week | 1 | 50 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 20.2.2 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 2 | 1675 | Risk Ratio (M-H, Fixed, 95% CI) | 2.18 [1.55, 3.07] |
| 20.2.3 Risedronate 2.5 mg/day vs Etidronate 200 mg/day | 1 | 207 | Risk Ratio (M-H, Fixed, 95% CI) | 0.21 [0.01, 4.32] |
| 20.2.4 Risedronate 2.5 mg/day vs Ibandronate 1 mg/month, IV | 1 | 626 | Risk Ratio (M-H, Fixed, 95% CI) | 1.17 [0.77, 1.79] |
| 20.2.5 Risedronate 2.5 mg/day vs Ibandronate 0.5 mg/month, IV | 1 | 633 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.65, 1.46] |
| 20.2.6 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 2 | 1706 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.64, 1.11] |

## Analysis 20.1. Comparison 20: Risedronate vs Active comparators-Radiographic vertebral fractures, Outcome 1: Treatment vs Reference, Primary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **20.1.1 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | |
| Harris 2001 (1) | 3 | 168 | 4 | 155 | 100.0% | 0.69 [0.16 , 3.04] |
| **Subtotal (95% CI)** | | **168** | | **155** | **100.0%** | **0.69 [0.16 , 3.04]** |
| Total events: | 3 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.49 (P = 0.63) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

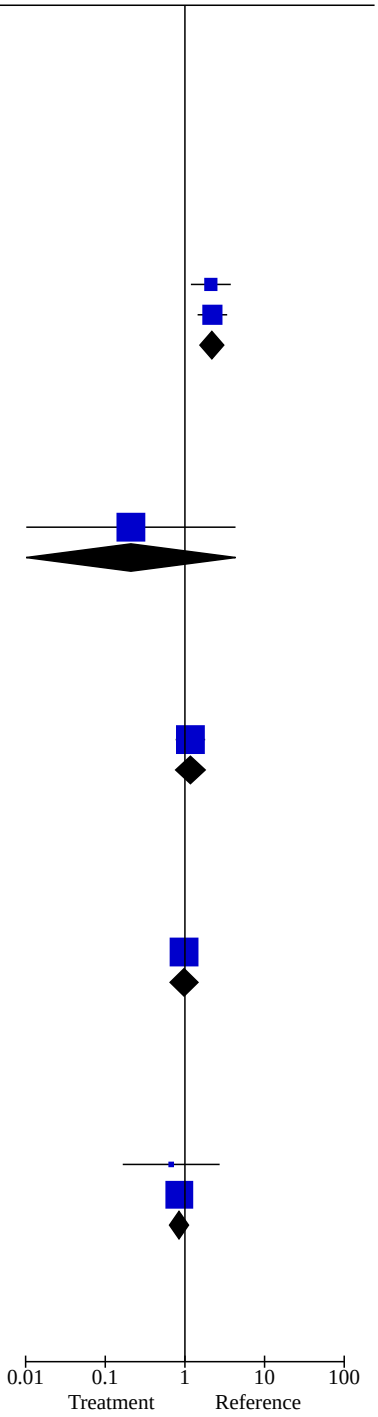



**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 20.2. Comparison 20: Risedronate vs Active comparators- Radiographic vertebral fractures, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **20.2.1 Risedronate 5 mg/day vs Alendronate 70 mg/week** | | | | | | |
| Sarioglu 2006 | 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 | | | | | | |
| **20.2.2 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Hadji 2012 | 33 | 309 | 16 | 317 | 35.7% | 2.12 [1.19 , 3.76] |
| Kendler 2018 | 64 | 533 | 28 | 516 | 64.3% | 2.21 [1.44 , 3.39] |
| **Subtotal (95% CI)** | | **842** | | **833** | **100.0%** | **2.18 [1.55 , 3.07]** |
| Total events: | 97 | | 44 | | | |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0% | | | | | | |
| Test for overall effect: Z = 4.45 (P < 0.00001) | | | | | | |
| **20.2.3 Risedronate 2.5 mg/day vs Etidronate 200 mg/day** | | | | | | |
| Fukunaga 2002 | 0 | 101 | 2 | 106 | 100.0% | 0.21 [0.01 , 4.32] |
| **Subtotal (95% CI)** | | **101** | | **106** | **100.0%** | **0.21 [0.01 , 4.32]** |
| Total events: | 0 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | | |
| **20.2.4 Risedronate 2.5 mg/day vs Ibandronate 1 mg/month, IV** | | | | | | |
| Nakamura 2013 | 40 | 309 | 35 | 317 | 100.0% | 1.17 [0.77 , 1.79] |
| **Subtotal (95% CI)** | | **309** | | **317** | **100.0%** | **1.17 [0.77 , 1.79]** |
| Total events: | 40 | | 35 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.73 (P = 0.46) | | | | | | |
| **20.2.5 Risedronate 2.5 mg/day vs Ibandronate 0.5 mg/month, IV** | | | | | | |
| Nakamura 2013 | 40 | 309 | 43 | 324 | 100.0% | 0.98 [0.65 , 1.46] |
| **Subtotal (95% CI)** | | **309** | | **324** | **100.0%** | **0.98 [0.65 , 1.46]** |
| Total events: | 40 | | 43 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.12 (P = 0.90) | | | | | | |
| **20.2.6 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day)** | | | | | | |
| Kasukawa 2014 | 3 | 29 | 4 | 26 | 4.2% | 0.67 [0.17 , 2.73] |
| Tanaka 2017 (1) | 83 | 841 | 94 | 810 | 95.8% | 0.85 [0.64 , 1.12] |
| **Subtotal (95% CI)** | | **870** | | **836** | **100.0%** | **0.84 [0.64 , 1.11]** |
| Total events: | 86 | | 98 | | | |
| Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | | |
| Test for subgroup differences: Chi² = 20.13, df = 4 (P = 0.0005), I² = 80.1% | | | | | | |




**Footnotes**

(1) Risedronate was provided daily at 2.5 mg or weekly at 17.5 mg.

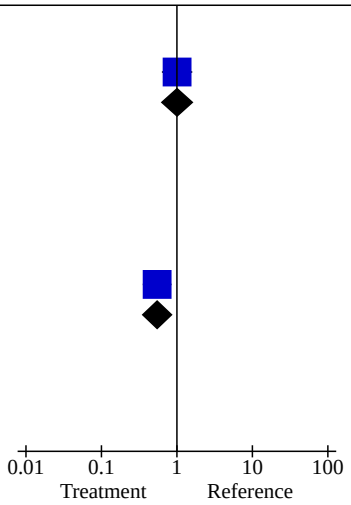
**Comparison 21. Risedronate vs Active comparators- Withdrawal due to adverse events**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 21.1 Treatment vs Reference, Primary | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 21.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 1 | 1053 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.63, 1.60] |
| 21.1.2 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.35, 0.85] |
| 21.2 Treatment vs Reference, Secondary | 13 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 21.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 4 | 1448 | Risk Ratio (M-H, Fixed, 95% CI) | 1.15 [0.82, 1.61] |
| 21.2.2 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | 4.33 [1.24, 15.10] |
| 21.2.3 Risedronate 35 mg/week vs Parathyroid hormone 1-84 100 µg/day, SC | 1 | 268 | Risk Ratio (M-H, Fixed, 95% CI) | 0.24 [0.07, 0.82] |
| 21.2.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 3 | 2120 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.58, 1.02] |
| 21.2.5 Risedronate 2.5 mg/day vs Etidronate 200 mg/day | 1 | 235 | Risk Ratio (M-H, Fixed, 95% CI) | 1.13 [0.42, 3.02] |
| 21.2.6 Risedronate 2.5 mg/day vs Teriparatide 20 µg/day, SC | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 21.2.7 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 2 | 1975 | Risk Ratio (M-H, Fixed, 95% CI) | 0.63 [0.41, 0.98] |

## Analysis 21.1. Comparison 21: Risedronate vs Active comparators- Withdrawal due to adverse events, Outcome 1: Treatment vs Reference, Primary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **21.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Rosen 2005 | 34 | 533 | 33 | 520 | 100.0% | 1.01 [0.63 , 1.60] |
| **Subtotal (95% CI)** | | **533** | | **520** | **100.0%** | **1.01 [0.63 , 1.60]** |
| Total events: | 34 | | 33 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.02 (P = 0.98) | | | | | | |
| **21.1.2 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | |
| Harris 2001 (1) | 27 | 263 | 49 | 261 | 100.0% | 0.55 [0.35 , 0.85] |
| **Subtotal (95% CI)** | | **263** | | **261** | **100.0%** | **0.55 [0.35 , 0.85]** |
| Total events: | 27 | | 49 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.70 (P = 0.007) | | | | | | |

Test for subgroup differences: $Chi^2 = 3.51$, df = 1 (P = 0.06), $I^2 = 71.5\%$

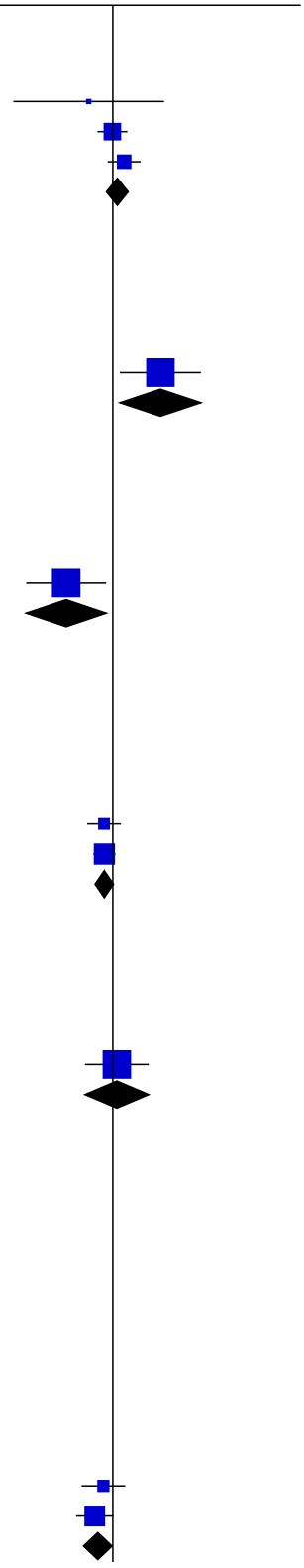



**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 21.2. Comparison 21: Risedronate vs Active comparators- Withdrawal due to adverse events, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **21.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Atmaca 2006 (1) | 0 | 14 | 0 | 16 | | Not estimable |
| Dobnig 2006 (1) | 1 | 21 | 2 | 20 | 3.6% | 0.48 [0.05 , 4.85] |
| Hosking 2003 (2) | 31 | 222 | 31 | 219 | 54.5% | 0.99 [0.62 , 1.57] |
| Reid 2006 | 34 | 468 | 24 | 468 | 41.9% | 1.42 [0.85 , 2.35] |
| **Subtotal (95% CI)** | | **725** | | **723** | **100.0%** | **1.15 [0.82 , 1.61]** |
| Total events: | 66 | | 57 | | | |
| Heterogeneity: Chi² = 1.63, df = 2 (P = 0.44); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | | | |
| **21.2.2 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC** | | | | | | |
| Roux 2014 | 13 | 429 | 3 | 429 | 100.0% | 4.33 [1.24 , 15.10] |
| **Subtotal (95% CI)** | | **429** | | **429** | **100.0%** | **4.33 [1.24 , 15.10]** |
| Total events: | 13 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.30 (P = 0.02) | | | | | | |
| **21.2.3 Risedronate 35 mg/week vs Parathyroid hormone 1-84 100 µg/day, SC** | | | | | | |
| NCT00365456 | 3 | 132 | 13 | 136 | 100.0% | 0.24 [0.07 , 0.82] |
| **Subtotal (95% CI)** | | **132** | | **136** | **100.0%** | **0.24 [0.07 , 0.82]** |
| Total events: | 3 | | 13 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.28 (P = 0.02) | | | | | | |
| **21.2.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Anastasilakis 2008a | 0 | 22 | 0 | 22 | | Not estimable |
| Hadji 2012 | 23 | 350 | 31 | 360 | 30.4% | 0.76 [0.45 , 1.28] |
| Kendler 2018 | 54 | 683 | 70 | 683 | 69.6% | 0.77 [0.55 , 1.08] |
| **Subtotal (95% CI)** | | **1055** | | **1065** | **100.0%** | **0.77 [0.58 , 1.02]** |
| Total events: | 77 | | 101 | | | |
| Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.82 (P = 0.07) | | | | | | |
| **21.2.5 Risedronate 2.5 mg/day vs Etidronate 200 mg/day** | | | | | | |
| Fukunaga 2002 | 8 | 118 | 7 | 117 | 100.0% | 1.13 [0.42 , 3.02] |
| **Subtotal (95% CI)** | | **118** | | **117** | **100.0%** | **1.13 [0.42 , 3.02]** |
| Total events: | 8 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.25 (P = 0.80) | | | | | | |
| **21.2.6 Risedronate 2.5 mg/day vs Teriparatide 20 µg/day, SC** | | | | | | |
| Ohtori 2013 | 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 | | | | | | |
| **21.2.7 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day)** | | | | | | |
| Kasukawa 2014 | 11 | 50 | 15 | 51 | 32.3% | 0.75 [0.38 , 1.47] |
| Tanaka 2017 (3) | 18 | 943 | 31 | 931 | 67.7% | 0.57 [0.32 , 1.02] |
| **Subtotal (95% CI)** | | **993** | | **982** | **100.0%** | **0.63 [0.41 , 0.98]** |



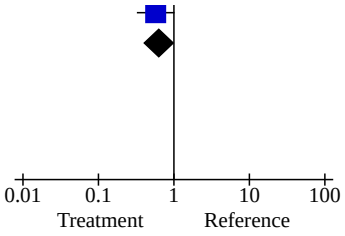
## Analysis 21.2. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Tanaka 2017 (3) | 18 | 943 | 31 | 931 | 67.7% | 0.57 [0.32 , 1.02] |
| **Subtotal (95% CI)** | | **993** | | **982** | **100.0%** | **0.63 [0.41 , 0.98]** |
| Total events: | 29 | | 46 | | | |

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%

Test for overall effect: Z = 2.06 (P = 0.04)

Test for subgroup differences: Chi² = 16.31, df = 5 (P = 0.006), I² = 69.3%




**Footnotes**

(1) risedonate 5 mg/day was compared with alendronate 10 mg/day

(2) risedonate 5 mg/day was compared with alendronate 70 mg/week

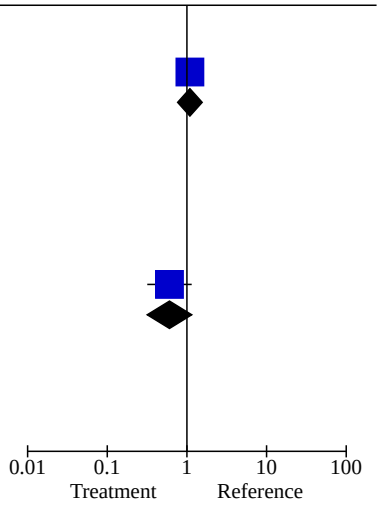
(3) Risedronate 2.5 mg/day or 17.5 mg/week was used.

## Comparison 22. Risedronate vs Active comparators- Serious adverse events

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 22.1 Treatment vs Reference, Primary | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 22.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 1 | 825 | Risk Ratio (M-H, Fixed, 95% CI) | 1.09 [0.77, 1.55] |
| 22.1.2 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.32, 1.15] |
| 22.2 Treatment vs Reference, Secondary | 11 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 22.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week* | 5 | 1475 | Risk Ratio (M-H, Fixed, 95% CI) | 1.11 [0.80, 1.54] |
| 22.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 1 | 115 | Risk Ratio (M-H, Fixed, 95% CI) | 1.12 [0.44, 2.89] |
| 22.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | 1.06 [0.67, 1.67] |
| 22.2.4 Risedronate 35 mg/week vs Raloxifen 60 mg/day | 1 | 80 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 22.2.5 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 3 | 2114 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.79, 1.14] |
| 22.2.6 Risedronate 2.5 mg/day vs Teriparatide 20 µg/day, SC | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 22.2.7 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 1 | 1874 | Risk Ratio (M-H, Fixed, 95% CI) | 1.13 [0.55, 2.30] |

## Analysis 22.1. Comparison 22: Risedronate vs Active comparators- Serious adverse events, Outcome 1: Treatment vs Reference, Primary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **22.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Rosen 2005 | 56 | 414 | 51 | 411 | 100.0% | 1.09 [0.77 , 1.55] |
| **Subtotal (95% CI)** | | **414** | | **411** | **100.0%** | **1.09 [0.77 , 1.55]** |
| Total events: | 56 | | 51 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | | |
| **22.1.2 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | |
| Harris 2001 (1) | 14 | 263 | 23 | 261 | 100.0% | 0.60 [0.32 , 1.15] |
| **Subtotal (95% CI)** | | **263** | | **261** | **100.0%** | **0.60 [0.32 , 1.15]** |
| Total events: | 14 | | 23 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.54 (P = 0.12) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.49$, df = 1 (P = 0.11), $I^2 = 59.9\%$ | | | | | | |

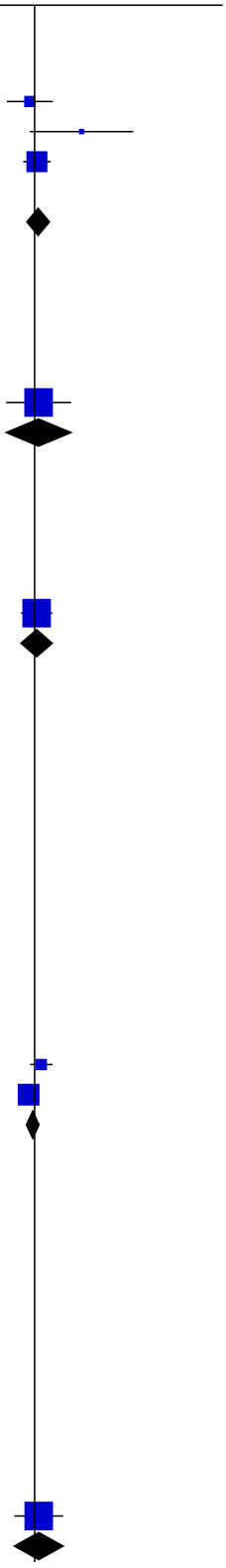



**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 22.2. Comparison 22: Risedronate vs Active comparators- Serious adverse events, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **22.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week*** | | | | | | |
| Atmaca 2006 (1) | 0 | 14 | 0 | 16 | | Not estimable |
| Hosking 2003 (2) | 15 | 222 | 17 | 219 | 28.2% | 0.87 [0.45 , 1.70] |
| Paggiosi 2014a | 8 | 58 | 2 | 57 | 3.3% | 3.93 [0.87 , 17.72] |
| Reid 2006 | 44 | 395 | 42 | 403 | 68.5% | 1.07 [0.72 , 1.59] |
| Yanik 2008 | 0 | 44 | 0 | 47 | | Not estimable |
| **Subtotal (95% CI)** | | **733** | | **742** | **100.0%** | **1.11 [0.80 , 1.54]** |
| Total events: | 67 | | 61 | | | |
| Heterogeneity: Chi² = 3.25, df = 2 (P = 0.20); I² = 38% | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | |
| **22.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month** | | | | | | |
| Paggiosi 2014a | 8 | 58 | 7 | 57 | 100.0% | 1.12 [0.44 , 2.89] |
| **Subtotal (95% CI)** | | **58** | | **57** | **100.0%** | **1.12 [0.44 , 2.89]** |
| Total events: | 8 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | |
| **22.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC** | | | | | | |
| Roux 2014 | 35 | 429 | 33 | 429 | 100.0% | 1.06 [0.67 , 1.67] |
| **Subtotal (95% CI)** | | **429** | | **429** | **100.0%** | **1.06 [0.67 , 1.67]** |
| Total events: | 35 | | 33 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.25 (P = 0.80) | | | | | | |
| **22.2.4 Risedronate 35 mg/week vs Raloxifen 60 mg/day** | | | | | | |
| Yanik 2008 | 0 | 44 | 0 | 36 | | Not estimable |
| **Subtotal (95% CI)** | | **44** | | **36** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **22.2.5 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Anastasilakis 2008a | 0 | 22 | 0 | 22 | | Not estimable |
| Hadji 2012 | 65 | 350 | 55 | 360 | 28.4% | 1.22 [0.88 , 1.69] |
| Kendler 2018 | 115 | 680 | 137 | 680 | 71.6% | 0.84 [0.67 , 1.05] |
| **Subtotal (95% CI)** | | **1052** | | **1062** | **100.0%** | **0.95 [0.79 , 1.14]** |
| Total events: | 180 | | 192 | | | |
| Heterogeneity: Chi² = 3.35, df = 1 (P = 0.07); I² = 70% | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | | |
| **22.2.6 Risedronate 2.5 mg/day vs Teriparatide 20 µg/day, SC** | | | | | | |
| Ohtori 2013 | 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 | | | | | | |
| **22.2.7 Risedronate 17.5 mg/week vs (Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day)** | | | | | | |
| Tanaka 2017 (3) | 16 | 943 | 14 | 931 | 100.0% | 1.13 [0.55 , 2.30] |
| **Subtotal (95% CI)** | | **943** | | **931** | **100.0%** | **1.13 [0.55 , 2.30]** |



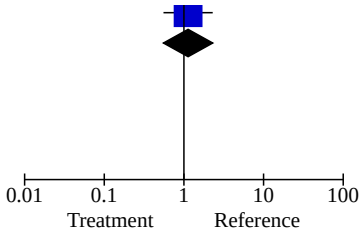
## Analysis 22.2. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Tanaka 2017 (3) | 16 | 943 | 14 | 931 | 100.0% | 1.13 [0.55 , 2.30] |
| **Subtotal (95% CI)** | | **943** | | **931** | **100.0%** | **1.13 [0.55 , 2.30]** |
| Total events: | 16 | | 14 | | | |

Heterogeneity: Not applicable

Test for overall effect: Z = 0.33 (P = 0.74)

Test for subgroup differences: Chi² = 0.95, df = 4 (P = 0.92), I² = 0%




**Footnotes**

(1) Risedonate 5 mg/day compared with alendronate 10 mg/day

(2) Risedonate 5 mg/day compared with alendronate 70 mg/week

(3) Risedronate 2.5 mg/d or 17.5 mg/wk was used in two arms

## Comparison 23. Risedronate vs Active comparators- Health-related quality of life

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 23.1 Treatment vs Reference, Secondary | 2 | | Std. Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 23.1.1 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 2 | 1960 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.01 [-0.10, 0.08] |

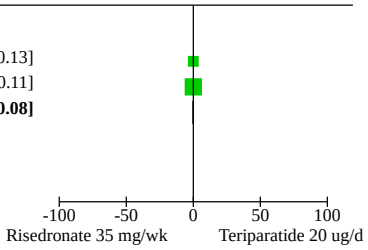
## Analysis 23.1. Comparison 23: Risedronate vs Active comparators- Health-related quality of life, Outcome 1: Treatment vs Reference, Secondary

| Study or Subgroup | Risedronate 35 mg/wk Mean | SD | Total | Teriparatide 20 ug/d Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **23.1.1 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | | | |
| Hadji 2012 | 5.17 | 22.78 | 327 | 5.67 | 23.55 | 344 | 34.2% | -0.02 [-0.17 , 0.13] |
| Kendler 2018 | 0.04 | 0.097 | 647 | 0.04 | 0.109 | 642 | 65.8% | 0.00 [-0.11 , 0.11] |
| **Subtotal (95% CI)** | | | **974** | | | **986** | **100.0%** | **-0.01 [-0.10 , 0.08]** |

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.16 (P = 0.87)

Test for subgroup differences: Not applicable



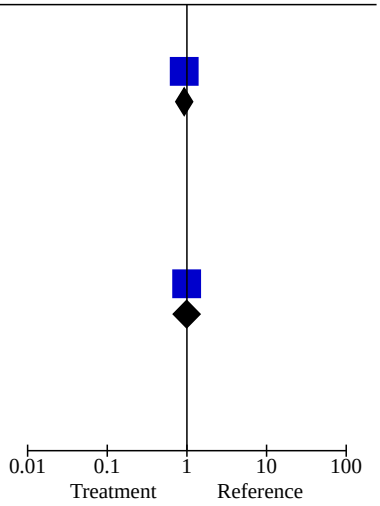

## Comparison 24. Risedronate vs Active comparators- Gastrointestinal adverse events

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 24.1 Treatment vs Reference, Primary | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 24.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 1 | 825 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.72, 1.18] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 24.1.2 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | 0.99 [0.67, 1.46] |
| 24.2 Treatment vs Reference, Secondary | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 24.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 2 | 1239 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.72, 1.08] |
| 24.2.2 Risedronate 2.5 mg/day vs Etidronate 200 mg/day | 1 | 235 | Risk Ratio (M-H, Fixed, 95% CI) | 1.16 [0.71, 1.91] |
| 24.2.3 Risedronate 17.5 mg/week vs (Risedronate17.5 mg/week+ Menatetrenone 45 mg/day) | 1 | 1874 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.38, 1.03] |

## Analysis 24.1. Comparison 24: Risedronate vs Active comparators-Gastrointestinal adverse events, Outcome 1: Treatment vs Reference, Primary

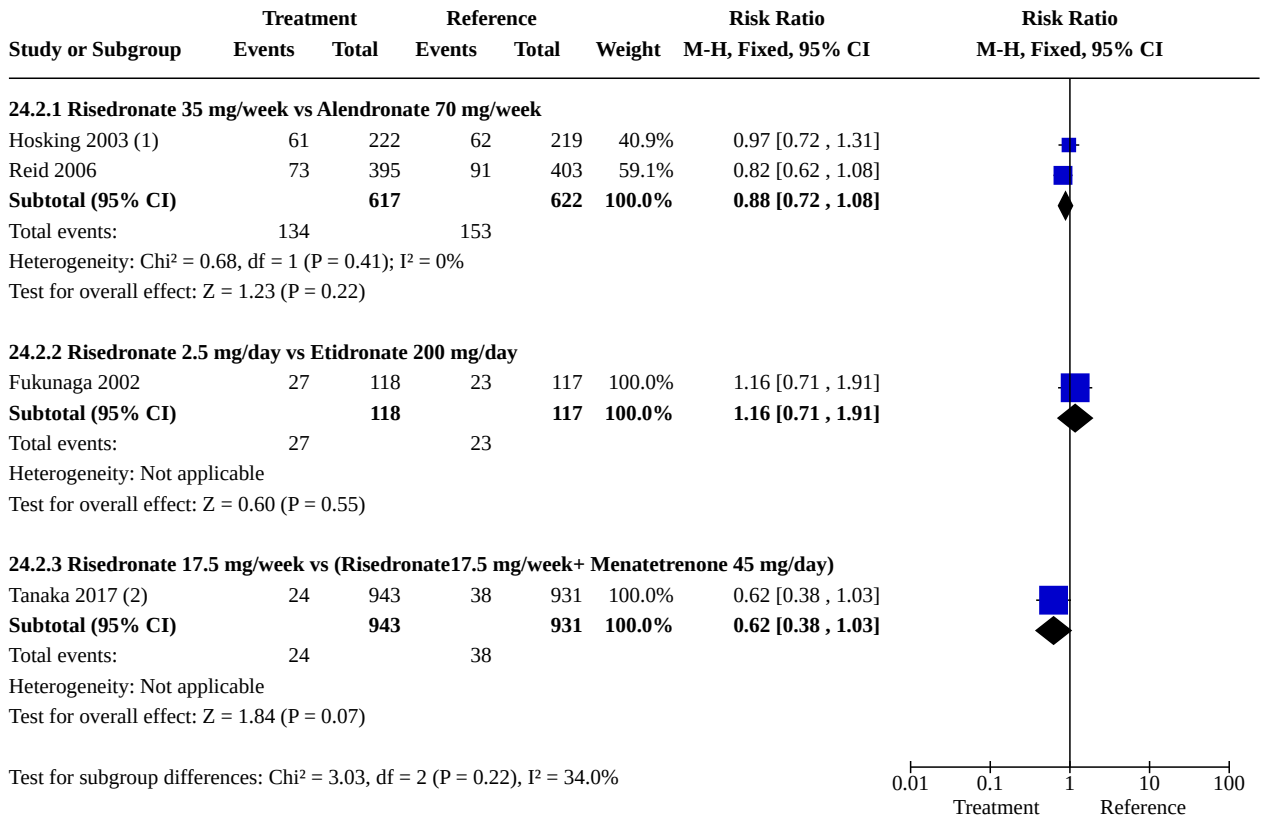
| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **24.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week** | | | | | | |
| Rosen 2005 | 95 | 414 | 102 | 411 | 100.0% | 0.92 [0.72 , 1.18] |
| **Subtotal (95% CI)** | | **414** | | **411** | **100.0%** | **0.92 [0.72 , 1.18]** |
| Total events: | 95 | | 102 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.63 (P = 0.53) | | | | | | |
| **24.1.2 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | |
| Harris 2001 (1) | 43 | 263 | 43 | 261 | 100.0% | 0.99 [0.67 , 1.46] |
| **Subtotal (95% CI)** | | **263** | | **261** | **100.0%** | **0.99 [0.67 , 1.46]** |
| Total events: | 43 | | 43 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | | |
| Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0% | | | | | | |




**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 24.2. Comparison 24: Risedronate vs Active comparators- Gastrointestinal adverse events, Outcome 2: Treatment vs Reference, Secondary




**Footnotes**

(1) Risedronate 5 mg/day was compared with alendronate 70 mg/week.

(2) Risedronate 2.5 mg/day or 17.5 mg/week was used in two arms.

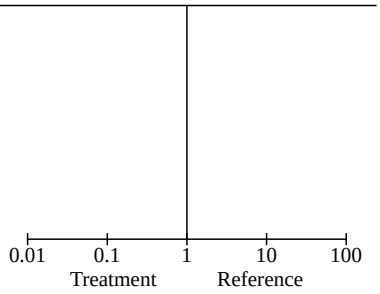
## Comparison 25. Risedronate vs Active comparators- Atypical femoral fractures

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 25.1 Treatment vs Reference, Primary | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 25.1.1 (Risedronate 5 mg/day+HRT) vs HRT | 1 | 524 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 25.2 Treatment vs Reference, Secondary | 7 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 25.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week* | 4 | 442 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 25.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 2 | 180 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 25.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 25.2.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 1 | 1360 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 25.2.5 Risedronate 2.5 mg/day vs Ibandronate 1 mg/month, IV | 1 | 752 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 25.2.6 Risedronate 2.5 mg/day vs Ibandronate 0.5 mg/month, IV | 1 | 760 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

**Analysis 25.1. Comparison 25: Risedronate vs Active comparators-Atypical femoral fractures, Outcome 1: Treatment vs Reference, Primary**

| | Treatment | | Reference | | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| **25.1.1 (Risedronate 5 mg/day+HRT) vs HRT** | | | | | | | |
| Harris 2001 (1) | 0 | 263 | 0 | 261 | | Not estimable | |
| **Subtotal (95% CI)** | | **263** | | **261** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

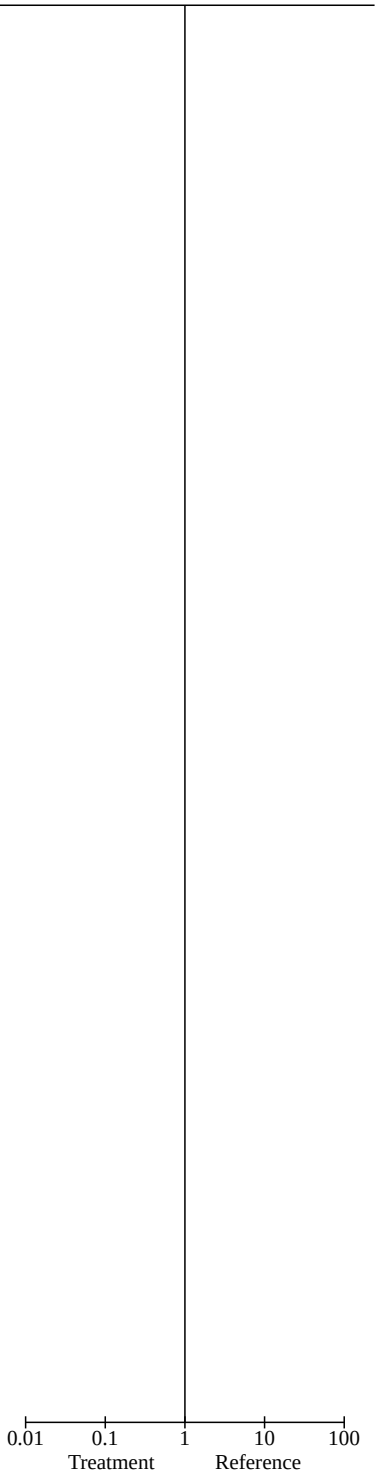



**Footnotes**

(1) HRT= conjugated equine estrogens 0.625 mg/day.

## Analysis 25.2. Comparison 25: Risedronate vs Active comparators- Atypical femoral fractures, Outcome 2: Treatment vs Reference, Secondary

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **25.2.1 Risedronate 35 mg/week vs Alendronate 70 mg/week*** | | | | | | |
| Akyol 2006 | 0 | 52 | 0 | 60 | | Not estimable |
| Galesanu 2011 | 0 | 32 | 0 | 133 | | Not estimable |
| Paggiosi 2014a | 0 | 58 | 0 | 57 | | Not estimable |
| Sarioglu 2006 (1) | 0 | 25 | 0 | 25 | | Not estimable |
| **Subtotal (95% CI)** | | **167** | | **275** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **25.2.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month** | | | | | | |
| Galesanu 2011 | 0 | 32 | 0 | 33 | | Not estimable |
| Paggiosi 2014a | 0 | 58 | 0 | 57 | | Not estimable |
| **Subtotal (95% CI)** | | **90** | | **90** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **25.2.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC** | | | | | | |
| Roux 2014 | 0 | 429 | 0 | 429 | | Not estimable |
| **Subtotal (95% CI)** | | **429** | | **429** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **25.2.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Kendler 2018 | 0 | 680 | 0 | 680 | | Not estimable |
| **Subtotal (95% CI)** | | **680** | | **680** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **25.2.5 Risedronate 2.5 mg/day vs Ibandronate 1 mg/month, IV** | | | | | | |
| Nakamura 2013 | 0 | 371 | 0 | 381 | | Not estimable |
| **Subtotal (95% CI)** | | **371** | | **381** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **25.2.6 Risedronate 2.5 mg/day vs Ibandronate 0.5 mg/month, IV** | | | | | | |
| Nakamura 2013 | 0 | 371 | 0 | 389 | | Not estimable |
| **Subtotal (95% CI)** | | **371** | | **389** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



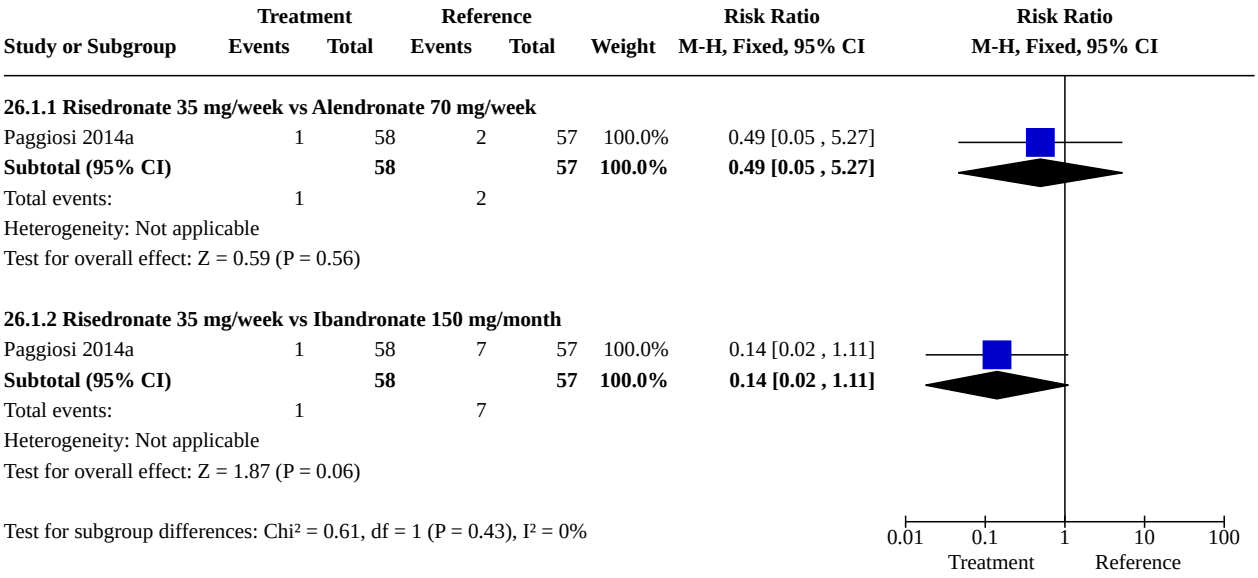

**Footnotes**

(1) Risedronated 5 mg/day was compared with alendronate 70 mg/week.

### Comparison 26. Risedronate vs Active comparators- Acute phase reaction

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 26.1 Treatment vs Reference, Secondary | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 26.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 1 | 115 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.05, 5.27] |
| 26.1.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 1 | 115 | Risk Ratio (M-H, Fixed, 95% CI) | 0.14 [0.02, 1.11] |

### Analysis 26.1. Comparison 26: Risedronate vs Active comparators- Acute phase reaction, Outcome 1: Treatment vs Reference, Secondary



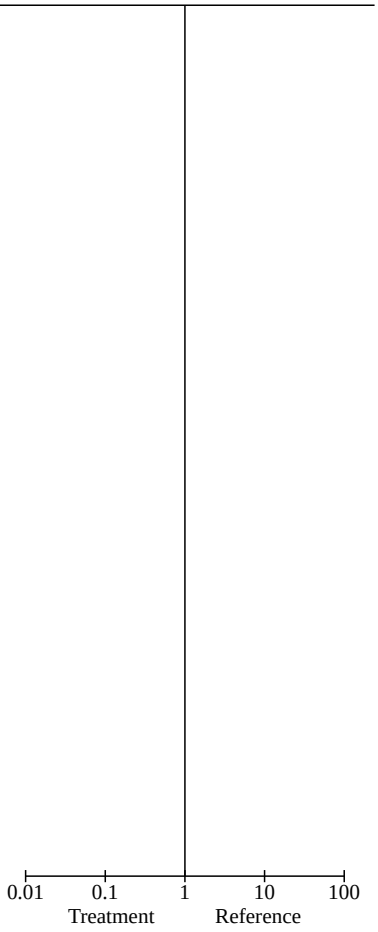

### Comparison 27. Risedronate vs Active comparators- Osteonecrosis of the jaw

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 27.1 Treatment vs Reference, Secondary | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 27.1.1 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 27.1.2 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 1 | 1360 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 27.1.3 Risedronate 2.5 mg/day vs Ibandronate 1 mg/month, IV | 1 | 752 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 27.1.4 Risedronate 2.5 mg/day vs Ibandronate 0.5 mg/month, IV | 1 | 760 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

**Analysis 27.1. Comparison 27: Risedronate vs Active comparators- Osteonecrosis of the jaw, Outcome 1: Treatment vs Reference, Secondary**

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **27.1.1 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC** | | | | | | |
| Roux 2014 | 0 | 429 | 0 | 429 | | Not estimable |
| **Subtotal (95% CI)** | | **429** | | **429** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **27.1.2 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC** | | | | | | |
| Kendler 2018 | 0 | 680 | 0 | 680 | | Not estimable |
| **Subtotal (95% CI)** | | **680** | | **680** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **27.1.3 Risedronate 2.5 mg/day vs Ibandronate 1 mg/month, IV** | | | | | | |
| Nakamura 2013 | 0 | 371 | 0 | 381 | | Not estimable |
| **Subtotal (95% CI)** | | **371** | | **381** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **27.1.4 Risedronate 2.5 mg/day vs Ibandronate 0.5 mg/month, IV** | | | | | | |
| Nakamura 2013 | 0 | 371 | 0 | 389 | | Not estimable |
| **Subtotal (95% CI)** | | **371** | | **389** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

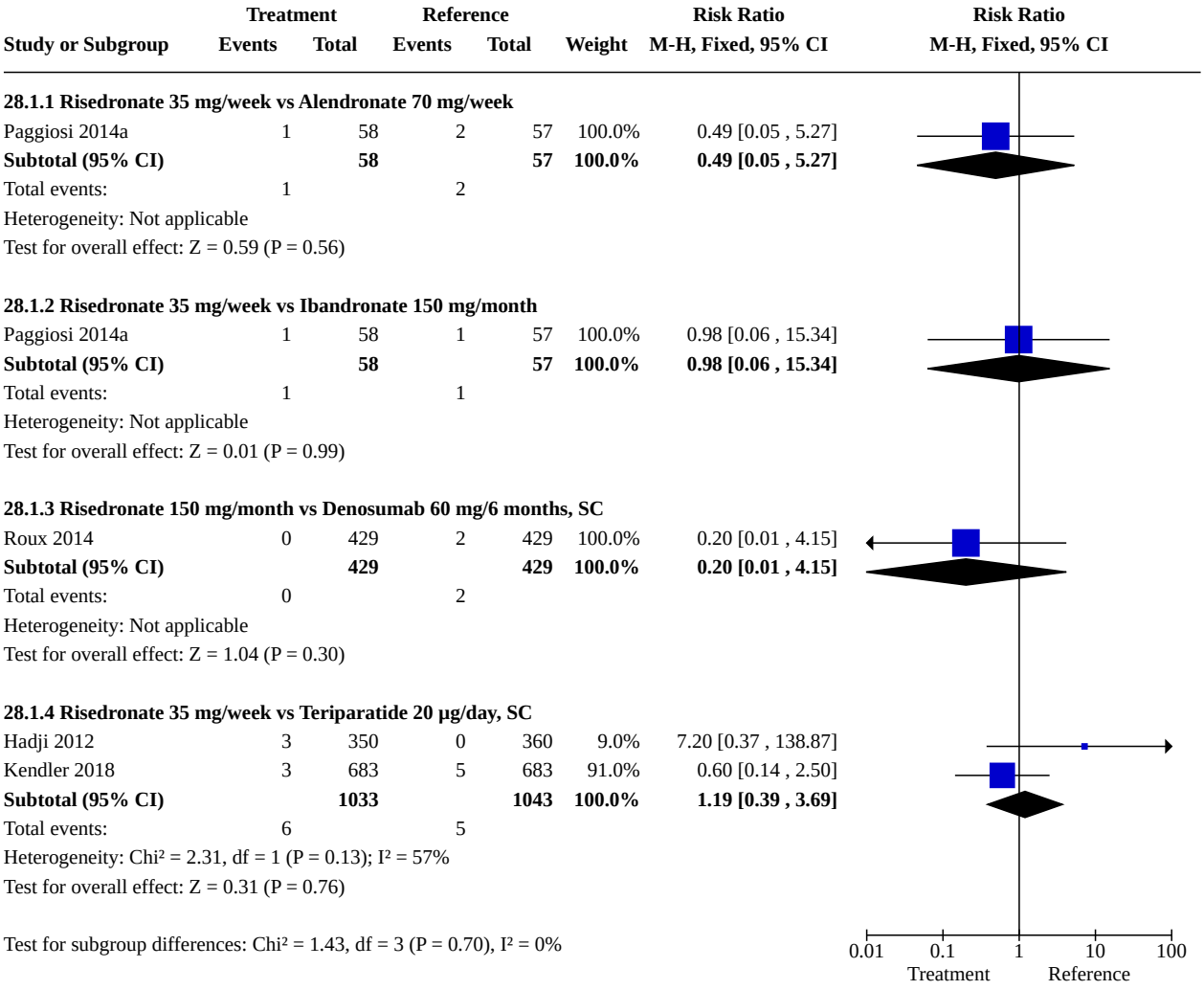



## Comparison 28. Risedronate vs Active comparators- Atrial fibrillation

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 28.1 Treatment vs Reference, Secondary | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 28.1.1 Risedronate 35 mg/week vs Alendronate 70 mg/week | 1 | 115 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.05, 5.27] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 28.1.2 Risedronate 35 mg/week vs Ibandronate 150 mg/month | 1 | 115 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.06, 15.34] |
| 28.1.3 Risedronate 150 mg/month vs Denosumab 60 mg/6 months, SC | 1 | 858 | Risk Ratio (M-H, Fixed, 95% CI) | 0.20 [0.01, 4.15] |
| 28.1.4 Risedronate 35 mg/week vs Teriparatide 20 µg/day, SC | 2 | 2076 | Risk Ratio (M-H, Fixed, 95% CI) | 1.19 [0.39, 3.69] |

**Analysis 28.1. Comparison 28: Risedronate vs Active comparators-Atrial fibrillation, Outcome 1: Treatment vs Reference, Secondary**



**Comparison 29. Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years**

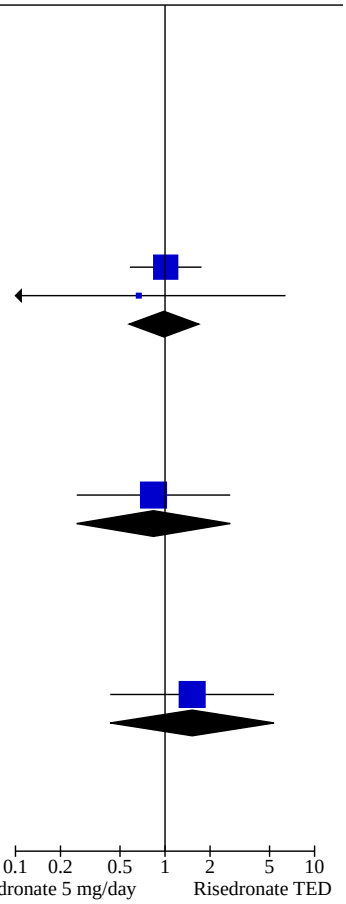
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 29.1 Clinical vertebral fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.1.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.1.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 2 | 1887 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.58, 1.68] |
| 29.1.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.26, 2.73] |
| 29.1.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [0.43, 5.36] |
| 29.2 Non-vertebral fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.2.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.2.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 2 | 1887 | Risk Ratio (M-H, Fixed, 95% CI) | 0.99 [0.71, 1.39] |
| 29.2.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.56, 1.42] |
| 29.2.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 0.90 [0.53, 1.53] |
| 29.3 Hip fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.3.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.3.2 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 5.06 [0.24, 105.24] |
| 29.4 Wrist fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.4.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.4.2 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.06, 16.15] |
| 29.5 Radiographic vertebral fractures | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.5.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 29.5.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 2 | 1740 | Risk Ratio (M-H, Fixed, 95% CI) | 1.62 [0.78, 3.35] |
| 29.5.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.47, 1.89] |
| 29.5.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1137 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.47, 1.97] |
| 29.6 Withdrawals due to adverse events | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.6.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.33, 1.98] |
| 29.6.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 2 | 1887 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.76, 1.24] |
| 29.6.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.81, 1.43] |
| 29.6.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.73, 1.28] |
| 29.7 Serious adverse events | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.7.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.23, 2.21] |
| 29.7.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 2 | 1887 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.80, 1.31] |
| 29.7.3 Risedronate 5 mg/day vs 75 mg*2days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.55, 1.00] |
| 29.7.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.48, 0.94] |
| 29.8 Gastrointestinal adverse events | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.8.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.51, 1.77] |
| 29.8.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 2 | 1887 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.74, 1.05] |
| 29.8.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 1.05 [0.87, 1.26] |
| 29.8.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.73, 1.07] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 29.9 Atypical femoral fracture | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.9.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.9.2 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.10 Acute phase reaction | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.10.1 Risedronate 5 mg/day vs 35 mg/week, Secondary | 1 | 922 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.23, 2.27] |
| 29.10.2 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | 0.11 [0.01, 2.07] |
| 29.10.3 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 0.11 [0.01, 0.89] |
| 29.11 Atrial fibrillation | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.11.1 Risedronate 5 mg/day vs 35 mg/week, Secondary | 1 | 922 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.02, 8.31] |
| 29.11.2 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | 0.58 [0.17, 1.97] |
| 29.12 Osteonecrosis of the jaw | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 29.12.1 Risedronate 5 mg/day vs 35 mg/week, Primary | 1 | 289 | Risk Ratio (M-H, Fixed, 95% CI) | 3.02 [0.12, 73.54] |
| 29.12.2 Risedronate 5 mg/day vs 35 mg/week, Secondary | 1 | 922 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.12.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary | 1 | 1229 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29.12.4 Risedronate 5 mg/day vs 150 mg/month, Secondary | 1 | 1292 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

## Analysis 29.1. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 1: Clinical vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.1.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 0 | 144 | 0 | 145 | | Not estimable |
| **Subtotal (95% CI)** | | **144** | | **145** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.1.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| Brown 2002 | 24 | 480 | 24 | 485 | 92.3% | 1.01 [0.58 , 1.75] |
| McClung 2012 (1) | 1 | 307 | 3 | 615 | 7.7% | 0.67 [0.07 , 6.39] |
| **Subtotal (95% CI)** | | **787** | | **1100** | **100.0%** | **0.98 [0.58 , 1.68]** |
| Total events: | 25 | | 27 | | | |
| Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.06 (P = 0.95) | | | | | | |
| **29.1.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 5 | 613 | 6 | 616 | 100.0% | 0.84 [0.26 , 2.73] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **0.84 [0.26 , 2.73]** |
| Total events: | 5 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | | |
| **29.1.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 6 | 642 | 4 | 650 | 100.0% | 1.52 [0.43 , 5.36] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **1.52 [0.43 , 5.36]** |
| Total events: | 6 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.52) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.51$, df = 2 (P = 0.78), $I^2 = 0\%$ | | | | | | |



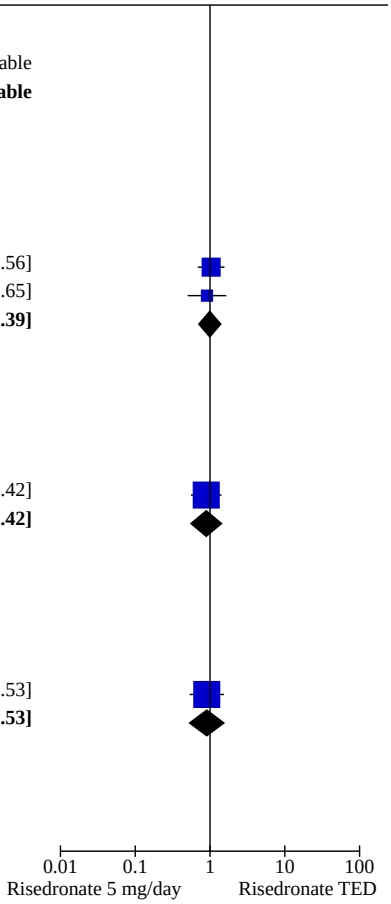

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.2. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 2: Non-vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.2.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 0 | 144 | 0 | 145 | | Not estimable |
| **Subtotal (95% CI)** | | **144** | | **145** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.2.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| Brown 2002 | 42 | 480 | 41 | 485 | 65.0% | 1.04 [0.69 , 1.56] |
| McClung 2012 (1) | 15 | 307 | 33 | 615 | 35.0% | 0.91 [0.50 , 1.65] |
| **Subtotal (95% CI)** | | **787** | | **1100** | **100.0%** | **0.99 [0.71 , 1.39]** |
| Total events: | 57 | | 74 | | | |
| Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | | | |
| **29.2.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 31 | 613 | 35 | 616 | 100.0% | 0.89 [0.56 , 1.42] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **0.89 [0.56 , 1.42]** |
| Total events: | 31 | | 35 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.49 (P = 0.63) | | | | | | |
| **29.2.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 25 | 642 | 28 | 650 | 100.0% | 0.90 [0.53 , 1.53] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **0.90 [0.53 , 1.53]** |
| Total events: | 25 | | 28 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.17$, df = 2 (P = 0.92), $I^2 = 0\%$ | | | | | | |



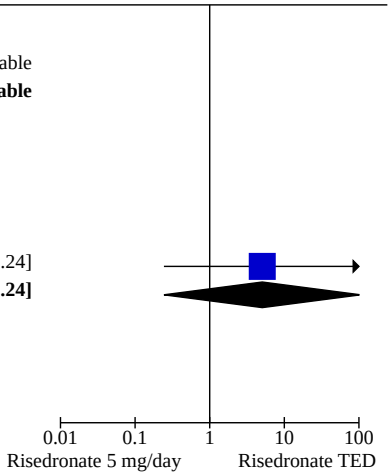

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

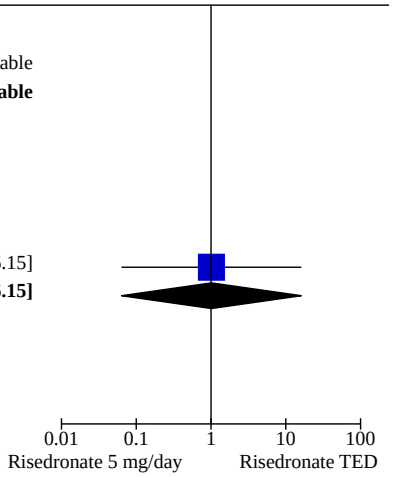
## Analysis 29.3. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 3: Hip fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.3.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 0 | 144 | 0 | 145 | | Not estimable |
| **Subtotal (95% CI)** | | **144** | | **145** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.3.2 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 2 | 642 | 0 | 650 | 100.0% | 5.06 [0.24 , 105.24] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **5.06 [0.24 , 105.24]** |
| Total events: | 2 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.29) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



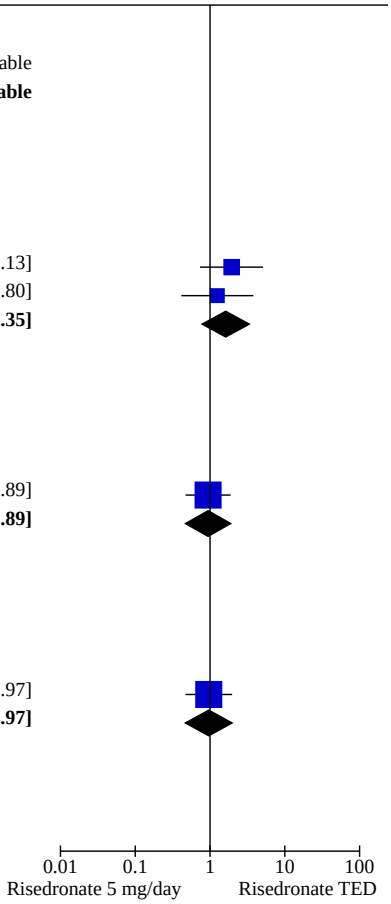

## Analysis 29.4. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 4: Wrist fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.4.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 0 | 144 | 0 | 145 | | Not estimable |
| **Subtotal (95% CI)** | | **144** | | **145** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.4.2 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 1 | 642 | 1 | 650 | 100.0% | 1.01 [0.06 , 16.15] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **1.01 [0.06 , 16.15]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.01 (P = 0.99) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



## Analysis 29.5. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 5: Radiographic vertebral fractures

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.5.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 0 | 144 | 0 | 145 | | Not estimable |
| **Subtotal (95% CI)** | | **144** | | **145** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.5.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| Brown 2002 | 12 | 415 | 6 | 403 | 53.3% | 1.94 [0.74 , 5.13] |
| McClung 2012 (1) | 5 | 307 | 8 | 615 | 46.7% | 1.25 [0.41 , 3.80] |
| **Subtotal (95% CI)** | | **722** | | **1018** | **100.0%** | **1.62 [0.78 , 3.35]** |
| Total events: | 17 | | 14 | | | |
| Heterogeneity: $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.30 (P = 0.19) | | | | | | |
| **29.5.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 15 | 613 | 16 | 616 | 100.0% | 0.94 [0.47 , 1.89] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **0.94 [0.47 , 1.89]** |
| Total events: | 15 | | 16 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.17 (P = 0.87) | | | | | | |
| **29.5.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 14 | 560 | 15 | 577 | 100.0% | 0.96 [0.47 , 1.97] |
| **Subtotal (95% CI)** | | **560** | | **577** | **100.0%** | **0.96 [0.47 , 1.97]** |
| Total events: | 14 | | 15 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.11 (P = 0.92) | | | | | | |
| Test for subgroup differences: $Chi^2 = 1.40$, df = 2 (P = 0.50), $I^2 = 0\%$ | | | | | | |



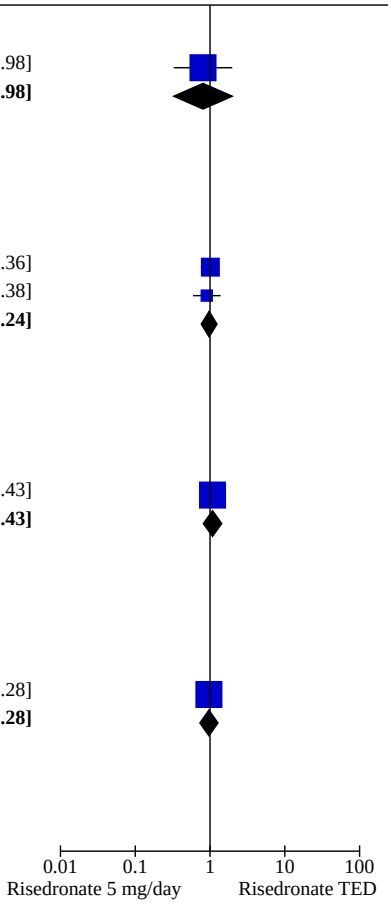

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.6. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 6: Withdrawals due to adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.6.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 8 | 144 | 10 | 145 | 100.0% | 0.81 [0.33 , 1.98] |
| **Subtotal (95% CI)** | | **144** | | **145** | **100.0%** | **0.81 [0.33 , 1.98]** |
| Total events: | 8 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | | | |
| **29.6.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| Brown 2002 | 75 | 480 | 75 | 485 | 64.4% | 1.01 [0.75 , 1.36] |
| McClung 2012 (1) | 28 | 307 | 62 | 615 | 35.6% | 0.90 [0.59 , 1.38] |
| **Subtotal (95% CI)** | | **787** | | **1100** | **100.0%** | **0.97 [0.76 , 1.24]** |
| Total events: | 103 | | 137 | | | |
| Heterogeneity: $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.22 (P = 0.82) | | | | | | |
| **29.6.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 86 | 613 | 80 | 616 | 100.0% | 1.08 [0.81 , 1.43] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **1.08 [0.81 , 1.43]** |
| Total events: | 86 | | 80 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.53 (P = 0.59) | | | | | | |
| **29.6.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 84 | 642 | 88 | 650 | 100.0% | 0.97 [0.73 , 1.28] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **0.97 [0.73 , 1.28]** |
| Total events: | 84 | | 88 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.61$, df = 3 (P = 0.89), $I^2 = 0\%$ | | | | | | |



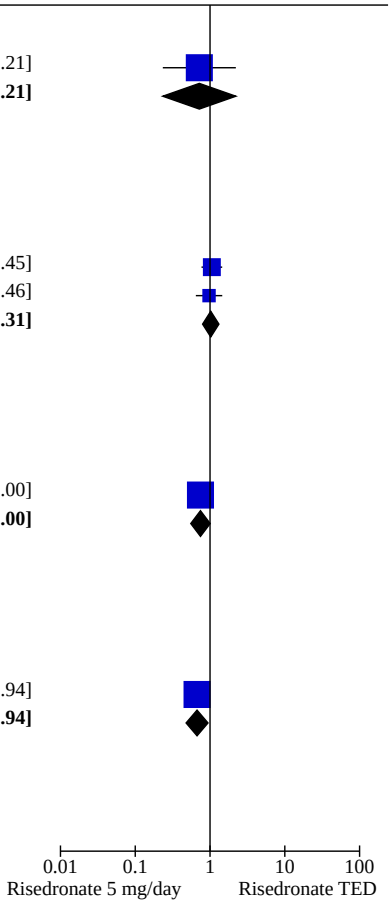

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.7. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 7: Serious adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.7.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 5 | 144 | 7 | 145 | 100.0% | 0.72 [0.23 , 2.21] |
| **Subtotal (95% CI)** | | **144** | | **145** | **100.0%** | **0.72 [0.23 , 2.21]** |
| Total events: | 5 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| **29.7.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| Brown 2002 | 67 | 480 | 64 | 485 | 59.9% | 1.06 [0.77 , 1.45] |
| McClung 2012 (1) | 31 | 307 | 64 | 615 | 40.1% | 0.97 [0.65 , 1.46] |
| **Subtotal (95% CI)** | | **787** | | **1100** | **100.0%** | **1.02 [0.80 , 1.31]** |
| Total events: | 98 | | 128 | | | |
| Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.18 (P = 0.86) | | | | | | |
| **29.7.3 Risedronate 5 mg/day vs 75 mg*2days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 66 | 613 | 89 | 616 | 100.0% | 0.75 [0.55 , 1.00] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **0.75 [0.55 , 1.00]** |
| Total events: | 66 | | 89 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.93 (P = 0.05) | | | | | | |
| **29.7.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 51 | 642 | 77 | 650 | 100.0% | 0.67 [0.48 , 0.94] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **0.67 [0.48 , 0.94]** |
| Total events: | 51 | | 77 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.33 (P = 0.02) | | | | | | |
| Test for subgroup differences: $Chi^2 = 4.77$, df = 3 (P = 0.19), $I^2 = 37.1\%$ | | | | | | |



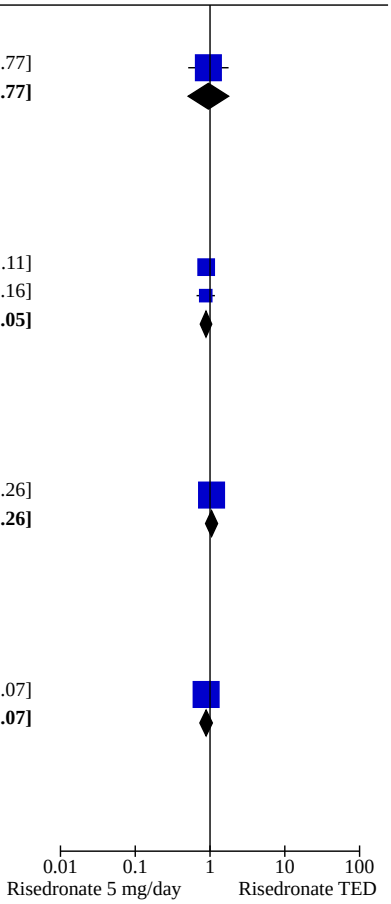

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.8. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 8: Gastrointestinal adverse events

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.8.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 17 | 144 | 18 | 145 | 100.0% | 0.95 [0.51 , 1.77] |
| **Subtotal (95% CI)** | | **144** | | **145** | **100.0%** | **0.95 [0.51 , 1.77]** |
| Total events: | 17 | | 18 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.16 (P = 0.87) | | | | | | |
| **29.8.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| Brown 2002 | 109 | 480 | 124 | 485 | 59.1% | 0.89 [0.71 , 1.11] |
| McClung 2012 (1) | 56 | 307 | 128 | 615 | 40.9% | 0.88 [0.66 , 1.16] |
| **Subtotal (95% CI)** | | **787** | | **1100** | **100.0%** | **0.88 [0.74 , 1.05]** |
| Total events: | 165 | | 252 | | | |
| Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | | | |
| **29.8.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 169 | 613 | 162 | 616 | 100.0% | 1.05 [0.87 , 1.26] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **1.05 [0.87 , 1.26]** |
| Total events: | 169 | | 162 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.50 (P = 0.62) | | | | | | |
| **29.8.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 148 | 642 | 169 | 650 | 100.0% | 0.89 [0.73 , 1.07] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **0.89 [0.73 , 1.07]** |
| Total events: | 148 | | 169 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.23 (P = 0.22) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.18$, df = 3 (P = 0.54), $I^2 = 0\%$ | | | | | | |



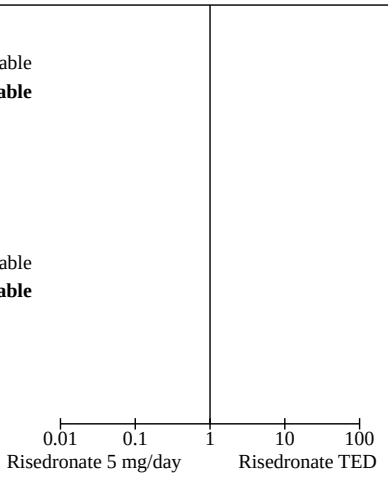

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.9. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 9: Atypical femoral fracture

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.9.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 0 | 144 | 0 | 145 | | Not estimable |
| **Subtotal (95% CI)** | | **144** | | **145** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.9.2 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (1) | 0 | 613 | 0 | 616 | | Not estimable |
| **Subtotal (95% CI)** | | **613** | | **616** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

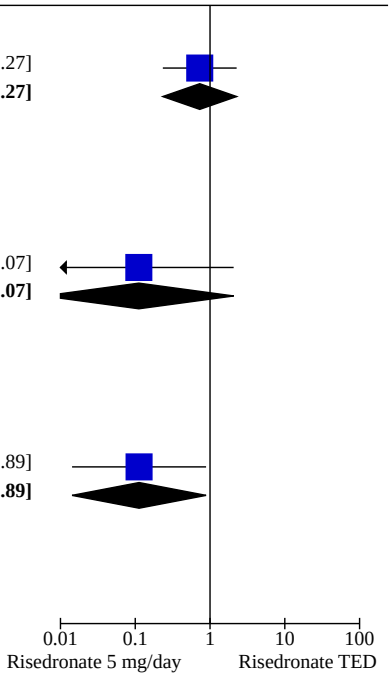



**Footnotes**

(1) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.10. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 10: Acute phase reaction

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.10.1 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| McClung 2012 (1) | 4 | 307 | 11 | 615 | 100.0% | 0.73 [0.23 , 2.27] |
| **Subtotal (95% CI)** | | **307** | | **615** | **100.0%** | **0.73 [0.23 , 2.27]** |
| Total events: | 4 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.55 (P = 0.58) | | | | | | |
| **29.10.2 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 0 | 613 | 4 | 616 | 100.0% | 0.11 [0.01 , 2.07] |
| **Subtotal (95% CI)** | | **613** | | **616** | **100.0%** | **0.11 [0.01 , 2.07]** |
| Total events: | 0 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.47 (P = 0.14) | | | | | | |
| **29.10.3 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 1 | 642 | 9 | 650 | 100.0% | 0.11 [0.01 , 0.89] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **0.11 [0.01 , 0.89]** |
| Total events: | 1 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.08 (P = 0.04) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.25, df = 2 (P = 0.20), $I^2$ = 38.5% | | | | | | |



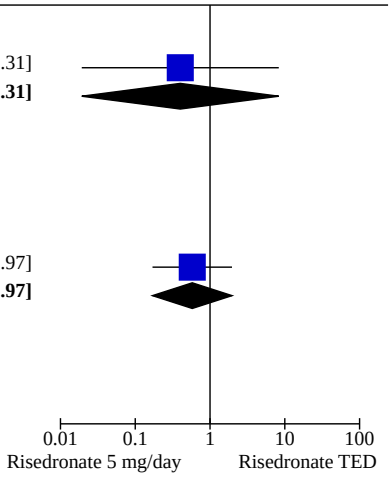

**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Analysis 29.11. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 11: Atrial fibrillation

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.11.1 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| McClung 2012 (1) | 0 | 307 | 2 | 615 | 100.0% | 0.40 [0.02 , 8.31] |
| **Subtotal (95% CI)** | | **307** | | **615** | **100.0%** | **0.40 [0.02 , 8.31]** |
| Total events: | 0 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.55) | | | | | | |
| **29.11.2 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 4 | 642 | 7 | 650 | 100.0% | 0.58 [0.17 , 1.97] |
| **Subtotal (95% CI)** | | **642** | | **650** | **100.0%** | **0.58 [0.17 , 1.97]** |
| Total events: | 4 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.88 (P = 0.38) | | | | | | |
| Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0% | | | | | | |

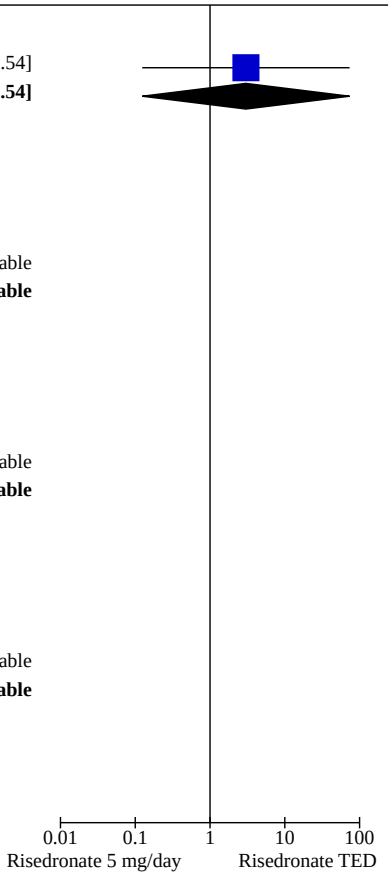



**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

## Analysis 29.12. Comparison 29: Risedronate 5 mg/day vs therapeutic equivalent dose (TED)- All years, Outcome 12: Osteonecrosis of the jaw

| Study or Subgroup | Risedronate 5 mg/day Events | Total | Risedronate TED Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **29.12.1 Risedronate 5 mg/day vs 35 mg/week, Primary** | | | | | | |
| Gu 2015 | 1 | 144 | 0 | 145 | 100.0% | 3.02 [0.12 , 73.54] |
| **Subtotal (95% CI)** | | **144** | | **145** | **100.0%** | **3.02 [0.12 , 73.54]** |
| Total events: | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | |
| **29.12.2 Risedronate 5 mg/day vs 35 mg/week, Secondary** | | | | | | |
| McClung 2012 (1) | 0 | 307 | 0 | 615 | | Not estimable |
| **Subtotal (95% CI)** | | **307** | | **615** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.12.3 Risedronate 5 mg/day vs 75 mg*2 days/month, Secondary** | | | | | | |
| Delmas 2008b (2) | 0 | 613 | 0 | 616 | | Not estimable |
| **Subtotal (95% CI)** | | **613** | | **616** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **29.12.4 Risedronate 5 mg/day vs 150 mg/month, Secondary** | | | | | | |
| Delmas 2008a | 0 | 642 | 0 | 650 | | Not estimable |
| **Subtotal (95% CI)** | | **642** | | **650** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Footnotes**

(1) The two delayed-released arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following brea

(2) Risedronate 75 mg on two consecutive days each month.

## Comparison 30. Risedronate at unapproved dose regimen

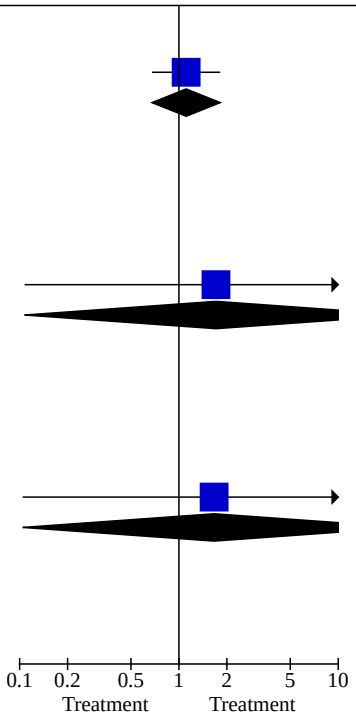
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 30.1 Clinical vertebral fractures | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.1.1 Risedronate 35 mg/week vs 50 mg/week, Secondary | 1 | 1456 | Risk Ratio (M-H, Fixed, 95% CI) | 1.11 [0.68, 1.82] |
| 30.1.2 Risedronate 2.5 mg/day vs 25 mg/month, Secondary | 1 | 539 | Risk Ratio (M-H, Fixed, 95% CI) | 1.71 [0.11, 27.16] |
| 30.1.3 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary | 1 | 530 | Risk Ratio (M-H, Fixed, 95% CI) | 1.66 [0.10, 26.44] |
| 30.2 Non-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 |
|---|---|---|---|---|
| 30.2.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary | 1 | 75 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.01, 8.14] |
| 30.2.2 Risedronate 35 mg/week vs 50 mg/week, Secondary | 1 | 1456 | Risk Ratio (M-H, Fixed, 95% CI) | 1.11 [0.77, 1.61] |
| 30.3 Hip fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.3.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary | 1 | 75 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 30.4 Wrist fractures | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.4.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary | 1 | 75 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.01, 8.14] |
| 30.5 Radiographic vertebral fractures | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.5.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary | 1 | 75 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.01, 8.14] |
| 30.5.2 Risedronate 35 mg/week vs 50 mg/week, Secondary | 1 | 1240 | Risk Ratio (M-H, Fixed, 95% CI) | 1.33 [0.56, 3.15] |
| 30.5.3 Risedronate 2.5 mg/day vs 25 mg/month, Secondary | 1 | 506 | Risk Ratio (M-H, Fixed, 95% CI) | 0.83 [0.25, 2.72] |
| 30.5.4 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary | 1 | 490 | Risk Ratio (M-H, Fixed, 95% CI) | 1.26 [0.34, 4.64] |
| 30.6 Withdrawals due to adverse events | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.6.1 Risedronate 35 mg/week vs 50 mg/week, Secondary | 1 | 1456 | Risk Ratio (M-H, Fixed, 95% CI) | 1.27 [0.96, 1.68] |
| 30.6.2 Risedronate 2.5 mg/day vs 25 mg/month, Secondary | 1 | 539 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.38, 1.34] |
| 30.6.3 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary | 1 | 531 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.40, 1.40] |
| 30.7 Serious adverse events | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.7.1 Risedronate 35 mg/week vs 50 mg/week, Secondary | 1 | 1456 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.65, 1.09] |
| 30.7.2 Risedronate 2.5 mg/day vs 25 mg/month, Secondary | 1 | 539 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.45, 1.75] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 30.7.3 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary | 1 | 530 | Risk Ratio (M-H, Fixed, 95% CI) | 1.54 [0.71, 3.30] |
| 30.8 Gastrointestinal adverse events | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 30.8.1 Risedronate 35 mg/week vs 50 mg/week, Secondary | 1 | 1456 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.80, 1.18] |

**Analysis 30.1. Comparison 30: Risedronate at unapproved dose regimen, Outcome 1: Clinical vertebral fractures**

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.1.1 Risedronate 35 mg/week vs 50 mg/week, Secondary** | | | | | | |
| Brown 2002 (1) | 48 | 965 | 22 | 491 | 100.0% | 1.11 [0.68 , 1.82] |
| **Subtotal (95% CI)** | | **965** | | **491** | **100.0%** | **1.11 [0.68 , 1.82]** |
| Total events: | 48 | | 22 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.42 (P = 0.68) | | | | | | |
| **30.1.2 Risedronate 2.5 mg/day vs 25 mg/month, Secondary** | | | | | | |
| NCT02063854 | 1 | 199 | 1 | 340 | 100.0% | 1.71 [0.11 , 27.16] |
| **Subtotal (95% CI)** | | **199** | | **340** | **100.0%** | **1.71 [0.11 , 27.16]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.38 (P = 0.70) | | | | | | |
| **30.1.3 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary** | | | | | | |
| NCT02063854 | 1 | 199 | 1 | 331 | 100.0% | 1.66 [0.10 , 26.44] |
| **Subtotal (95% CI)** | | **199** | | **331** | **100.0%** | **1.66 [0.10 , 26.44]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | | |
| Test for subgroup differences: Chi² = 0.16, df = 2 (P = 0.92), I² = 0% | | | | | | |

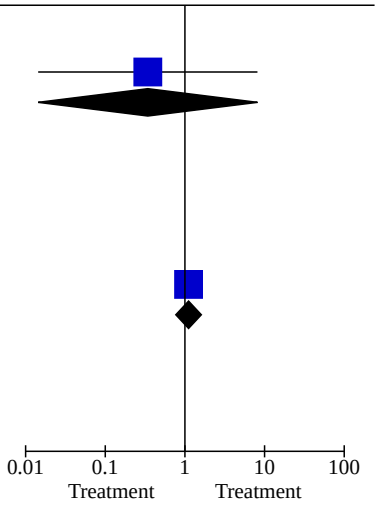



**Footnotes**

(1) Risedronate 35 mg/week: Arm of Risedronate 35 mg/week and Risedronate 5 mg/day are combined.

## Analysis 30.2. Comparison 30: Risedronate at unapproved dose regimen, Outcome 2: Non-vertebral fractures

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.2.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary** | | | | | | |
| Mortensen 1998 (1) | 0 | 37 | 1 | 38 | 100.0% | 0.34 [0.01 , 8.14] |
| **Subtotal (95% CI)** | | **37** | | **38** | **100.0%** | **0.34 [0.01 , 8.14]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |
| **30.2.2 Risedronate 35 mg/week vs 50 mg/week, Secondary** | | | | | | |
| Brown 2002 (2) | 83 | 965 | 38 | 491 | 100.0% | 1.11 [0.77 , 1.61] |
| **Subtotal (95% CI)** | | **965** | | **491** | **100.0%** | **1.11 [0.77 , 1.61]** |
| Total events: | 83 | | 38 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.56 (P = 0.57) | | | | | | |
| Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0% | | | | | | |

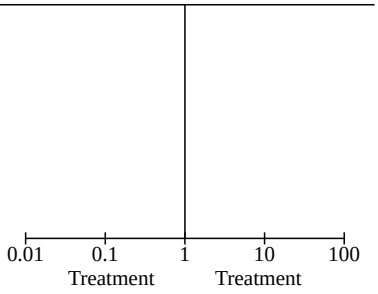



**Footnotes**

(1) Risedronate 5 mg/day, cyclic= Risedronate 5 mg daily for the first 2 weeks of every calendar month and placebo daily for the rest of the month.
(2) Risedronate 35 mg/week: Arm of Risedronate 35 mg/week and Risedronate 5 mg/day are combined.

## Analysis 30.3. Comparison 30: Risedronate at unapproved dose regimen, Outcome 3: Hip fractures

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.3.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary** | | | | | | |
| Mortensen 1998 (1) | 0 | 37 | 0 | 38 | | Not estimable |
| **Subtotal (95% CI)** | | **37** | | **38** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

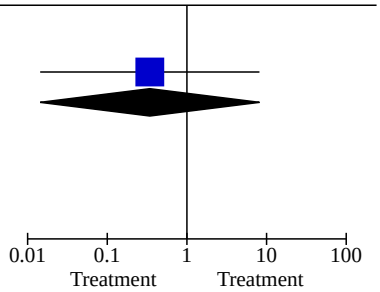



**Footnotes**

(1) Risedronate 5 mg/day, cyclic= Risedronate 5 mg daily for the first 2 weeks of every calendar month and placebo daily for the rest of the month.

## Analysis 30.4. Comparison 30: Risedronate at unapproved dose regimen, Outcome 4: Wrist fractures

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.4.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary** | | | | | | |
| Mortensen 1998 (1) | 0 | 37 | 1 | 38 | 100.0% | 0.34 [0.01 , 8.14] |
| **Subtotal (95% CI)** | | **37** | | **38** | **100.0%** | **0.34 [0.01 , 8.14]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

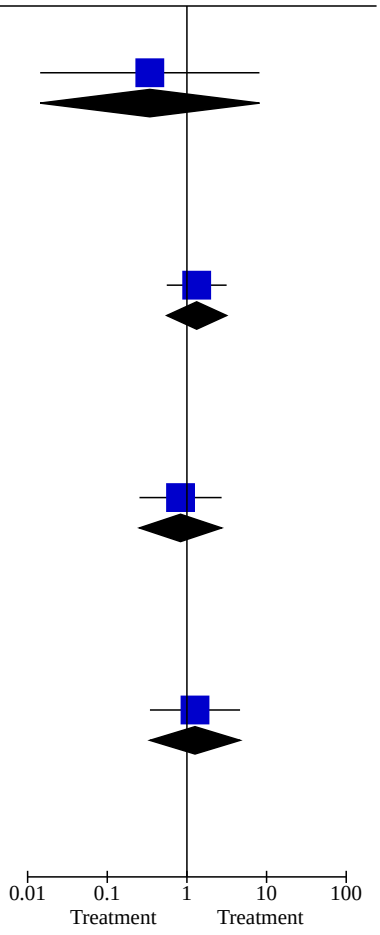



**Footnotes**

(1) Risedronate 5 mg/day, cyclic= Risedronate 5 mg daily for the first 2 weeks of every calendar month and placebo daily for the rest of the month.

## Analysis 30.5. Comparison 30: Risedronate at unapproved dose regimen, Outcome 5: Radiographic vertebral fractures

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.5.1 Risedronate 5 mg/day vs 5 mg/day, cyclic, Primary** | | | | | | |
| Mortensen 1998 (1) | 0 | 37 | 1 | 38 | 100.0% | 0.34 [0.01 , 8.14] |
| **Subtotal (95% CI)** | | **37** | | **38** | **100.0%** | **0.34 [0.01 , 8.14]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |
| **30.5.2 Risedronate 35 mg/week vs 50 mg/week, Secondary** | | | | | | |
| Brown 2002 (2) | 18 | 818 | 7 | 422 | 100.0% | 1.33 [0.56 , 3.15] |
| **Subtotal (95% CI)** | | **818** | | **422** | **100.0%** | **1.33 [0.56 , 3.15]** |
| Total events: | 18 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.64 (P = 0.52) | | | | | | |
| **30.5.3 Risedronate 2.5 mg/day vs 25 mg/month, Secondary** | | | | | | |
| NCT02063854 | 4 | 190 | 8 | 316 | 100.0% | 0.83 [0.25 , 2.72] |
| **Subtotal (95% CI)** | | **190** | | **316** | **100.0%** | **0.83 [0.25 , 2.72]** |
| Total events: | 4 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.76) | | | | | | |
| **30.5.4 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary** | | | | | | |
| NCT02063854 | 4 | 190 | 5 | 300 | 100.0% | 1.26 [0.34 , 4.64] |
| **Subtotal (95% CI)** | | **190** | | **300** | **100.0%** | **1.26 [0.34 , 4.64]** |
| Total events: | 4 | | 5 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.73) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.96, df = 3 (P = 0.81), $I^2$ = 0% | | | | | | |

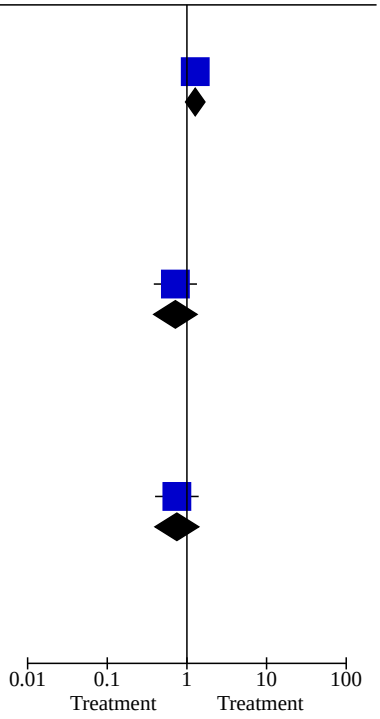



**Footnotes**

(1) Risedronate 5 mg/day, cyclic= Risedronate 5 mg daily for the first 2 weeks of every calendar month and placebo daily for the rest of the month.
(2) Risedronate 35 mg/week: Arm of Risedronate 35 mg/week and Risedronate 5 mg/day are combined.

## Analysis 30.6. Comparison 30: Risedronate at unapproved dose regimen, Outcome 6: Withdrawals due to adverse events

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.6.1 Risedronate 35 mg/week vs 50 mg/week, Secondary** | | | | | | |
| Brown 2002 (1) | 150 | 965 | 60 | 491 | 100.0% | 1.27 [0.96 , 1.68] |
| **Subtotal (95% CI)** | | **965** | | **491** | **100.0%** | **1.27 [0.96 , 1.68]** |
| Total events: | 150 | | 60 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.69 (P = 0.09) | | | | | | |
| **30.6.2 Risedronate 2.5 mg/day vs 25 mg/month, Secondary** | | | | | | |
| NCT02063854 | 13 | 199 | 31 | 340 | 100.0% | 0.72 [0.38 , 1.34] |
| **Subtotal (95% CI)** | | **199** | | **340** | **100.0%** | **0.72 [0.38 , 1.34]** |
| Total events: | 13 | | 31 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.05 (P = 0.29) | | | | | | |
| **30.6.3 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary** | | | | | | |
| NCT02063854 | 13 | 199 | 29 | 332 | 100.0% | 0.75 [0.40 , 1.40] |
| **Subtotal (95% CI)** | | **199** | | **332** | **100.0%** | **0.75 [0.40 , 1.40]** |
| Total events: | 13 | | 29 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.90 (P = 0.37) | | | | | | |
| Test for subgroup differences: $Chi^2 = 4.29$, df = 2 (P = 0.12), $I^2 = 53.4\%$ | | | | | | |

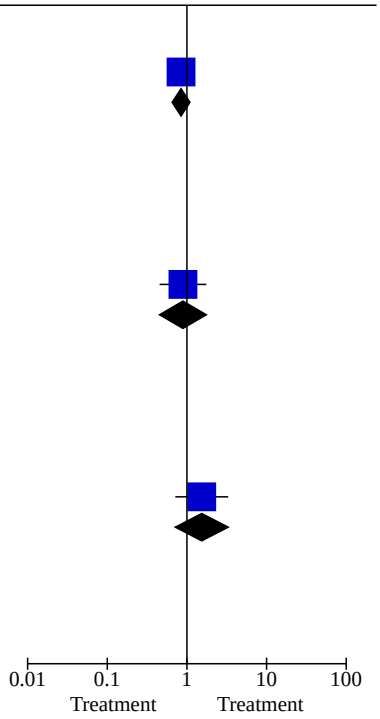



**Footnotes**

(1) Risedronate 35 mg/week: Arm of Risedronate 35 mg/week and Risedronate 5 mg/day are combined.

## Analysis 30.7. Comparison 30: Risedronate at unapproved dose regimen, Outcome 7: Serious adverse events

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.7.1 Risedronate 35 mg/week vs 50 mg/week, Secondary** | | | | | | |
| Brown 2002 (1) | 131 | 965 | 79 | 491 | 100.0% | 0.84 [0.65 , 1.09] |
| **Subtotal (95% CI)** | | **965** | | **491** | **100.0%** | **0.84 [0.65 , 1.09]** |
| Total events: | 131 | | 79 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.30 (P = 0.20) | | | | | | |
| **30.7.2 Risedronate 2.5 mg/day vs 25 mg/month, Secondary** | | | | | | |
| NCT02063854 | 12 | 199 | 23 | 340 | 100.0% | 0.89 [0.45 , 1.75] |
| **Subtotal (95% CI)** | | **199** | | **340** | **100.0%** | **0.89 [0.45 , 1.75]** |
| Total events: | 12 | | 23 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | | | |
| **30.7.3 Risedronate 2.5 mg/day vs 37.5 mg/month, Secondary** | | | | | | |
| NCT02063854 | 12 | 199 | 13 | 331 | 100.0% | 1.54 [0.71 , 3.30] |
| **Subtotal (95% CI)** | | **199** | | **331** | **100.0%** | **1.54 [0.71 , 3.30]** |
| Total events: | 12 | | 13 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.10 (P = 0.27) | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.12$, df = 2 (P = 0.35), $I^2 = 5.5\%$ | | | | | | |

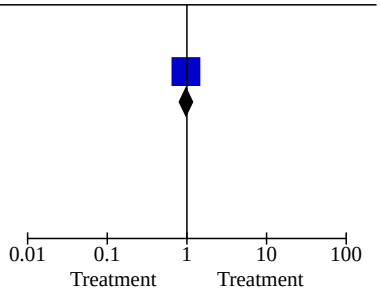



**Footnotes**

(1) Risedronate 35 mg/week: Arm of Risedronate 35 mg/week and Risedronate 5 mg/day are combined.

## Analysis 30.8. Comparison 30: Risedronate at unapproved dose regimen, Outcome 8: Gastrointestinal adverse events

| Study or Subgroup | Treatment Events | Treatment Total | Reference Events | Reference Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **30.8.1 Risedronate 35 mg/week vs 50 mg/week, Secondary** | | | | | | |
| Brown 2002 (1) | 233 | 965 | 122 | 491 | 100.0% | 0.97 [0.80 , 1.18] |
| **Subtotal (95% CI)** | | **965** | | **491** | **100.0%** | **0.97 [0.80 , 1.18]** |
| Total events: | 233 | | 122 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.77) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




**Footnotes**

(1) Risedronate 35 mg/week: Arm of Risedronate 35 mg/week and Risedronate 5 mg/day are combined.

## ADDITIONAL TABLES

**Table 1. Classification of primary and secondary prevention studies**

| CLASSIFICATION: | CLASSIFICATION CRITERIA ASSESSED: | | | | | | TOTAL STUDIES CLASSIFIED |
|---|---|---|---|---|---|---|---|
| | 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=33)** | | | | | | | |
| **Primary** | 0 | 1 | NA | 2 | 5 | 7 | **7** |
| **Secondary** | 18 | 5 | 3 | 13 | 11 | 3 | **26** |
| **Number of included studies excluded from quantitative analysis (k=10‡ )** | | | | | | | |
| **Primary** | 0 | 0 | NA | 0 | 0 | 2 | **2** |
| **Secondary** | 3 | 1 | 4 | 0 | 6 | 7 | **7** |

*Diagnosis of osteopenia for primary prevention trials, and osteoporosis for secondary prevention trials, following the diagnostic criteria of WHO 1994.
† BMD T-score, lumbar spine or total hip: > -2.5 for primary prevention trials, and ≤ -2.5 for secondary prevention trials.
‡ One study (Lim 2017) was undefined for insufficient information.
BMD: Bone mineral density; NA= not available; VF: vertebral fractures.

**Table 2. Relative risk of major outcomes after risedronate 5 mg/day versus placebo**

| Fracture sites | Primary / Secondary Prevention | # of Studies | # of Participants (risedronate / placebo) | Relative Risk (95% CI) | Association P value | Heterogeneity P value |
|---|---|---|---|---|---|---|
| Clinical vertebral | Primary | 1 | 115 / 55 | NE | NA | NA |
| | Secondary | 2 | 59 / 60 | NE | NA | NA |
| Non-vertebral | Primary | 3 | 281 / 216 | 0.54 (0.22, 1.35) | 0.19 | 0.52 |
| | Secondary | 6 | 7614 / 4559 | ***0.80 (0.72, 0.90)*** | 0.0002 | 0.44 |
| Hip | Primary | 2 | 152 / 91 | NE | NA | NA |
| | Secondary | 3 | 6256 / 3194 | ***0.73 (0.56, 0.94)*** | 0.02 | NA |
| Wrist | Primary | 2 | 152 / 91 | 0.48 (0.03, 7.50) | 0.60 | NA |
| | Secondary | 3 | 871 / 875 | 0.64 (0.33, 1.24) | 0.19 | NA |
| Withdrawals due to adverse events | Primary | 3 | 465 / 283 | 0.67 (0.38, 1.18) | 0.16 | 0.77 |
| | Secondary | 8 | 4815 / 4714 | 0.98 (0.90, 1.07) | 0.70 | 0.63 |
| Serious adverse events | Primary | 2 | 244 / 180 | 0.74 (0.42, 1.30) * | 0.87 | 0.07 |
| | Secondary | 6 | 4757 / 4678 | 1.00 (0.94 1.07) | 0.89 | 0.34 |

CI=Confidence Interval; NA=Not applicable; NE=Not estimable.
* $I^2$=70 % and non-significant test for heterogeneity P value=0.07; Relative Risk 0.90 (95% CI 0.26,3.15) estimated by random-effects model.

**Table 3. Five-year risks of fracture reduced after risedronate (by fracture index), Secondary prevention**

| Risedronate dose | Fracture Site Prevention RR (95% CI) | FRACTURE Index* | Risk* (untreated) | Risk (treated) | RRR | ARR | NNT |
|---|---|---|---|---|---|---|---|
| **Risedronate 5 mg/day** | Non-vertebral ***0.80 (0.72, 0.90)*** | 1-2 | 8.6% | 6.9% | 0.20 | 1.7% | 58 |
| | | 3-4 | 13.1% | 10.5% | 0.20 | 2.6% | 38 |
| | | 5 | 16.5% | 13.2% | 0.20 | 3.3% | 30 |
| | | 6-7 | 19.8% | 15.8% | 0.20 | 4.0% | 25 |
| | | 8-13 | 27.5% | 22.0% | 0.20 | 5.5% | 18 |
| | Hip ***0.73 (0.56, 0.94)*** | 1-2 | 0.4% | 0.3% | 0.27 | 0.1% | 926 |
| | | 3-4 | 0.9% | 0.7% | 0.27 | 0.2% | 412 |
| | | 5 | 1.9% | 1.4% | 0.27 | 0.5% | 195 |
| | | 6-7 | 3.9% | 2.8% | 0.27 | 1.1% | 95 |
| | | 8-13 | 8.7% | 6.4% | 0.27 | 2.3% | 43 |
| | Radiographic Vertebral ***0.61 (0.50, 0.75)*** | 1-2 | 1.2% | 0.7% | 0.39 | 0.5% | 214 |
| | | 3-4 | 2.5% | 1.5% | 0.39 | 1.0% | 103 |
| | | 5 | 5.3% | 3.2% | 0.39 | 2.1% | 48 |
| | | 6-7 | 7.1% | 4.3% | 0.39 | 2.8% | 36 |
| | | 8-13 | 11.2% | 6.8% | 0.39 | 4.4% | 23 |
| **Risedronate 2.5 mg/day** | Radiographic Vertebral ***0.63 (0.45, 0.87)*** | 1-2 | 1.2% | 0.8% | 0.37 | 0.4% | 225 |
| | | 3-4 | 2.5% | 1.4% | 0.37 | 0.9% | 108 |
| | | 5 | 5.3% | 2.9% | 0.37 | 2.0% | 51 |

**Table 3. Five-year risks of fracture reduced after risedronate (by fracture index), Secondary prevention** *(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| 6-7 | 7.1% | 3.8% | 0.37 | 2.6% | 38 |
| 8-13 | 11.2% | 6.0% | 0.37 | 4.1% | 24 |

RR=Relative Risk; CI=Confidence Interval; RRR=Relative Risk Reduction; ARR=Absolute Risk Reduction; NNT=Number Needed to Treat.
* Five-year risk of fractures by Quintile of the FRACTURE Index (FI) score (Black 2001).

**Table 4. Five-year age-specific absolute risk reduction (number need to treat) of first and subsequent fracture after risedronate 5 mg/day, Secondary prevention**

| Age Group (years) | Fracture | Risedronate 5 mg/day | | | Risedronate 2.5 mg/day |
|---|---|---|---|---|---|
| | | Non-vertebral *0.80 (0.72, 0.90)* | Hip *0.73 (0.56, 0.94)* | Radiographic vertebral *0.61 (0.50, 0.75)* | Radiographic vertebral *0.63 (0.45, 0.87)* |
| 50-54 | First | 0.3% (313) | 0.0% (NE) | 0.1% (1282) | 0.1% (1351) |
| | Subsequent | 0.5% (192) | 0.0% (NE) | 0.2% (513) | 0.2% (541) |
| 55-59 | First | 0.4% (238) | 0.1% (1852) | 0.2% (641) | 0.1% (676) |
| | Subsequent | 0.7% (147) | 0.11% (926) | 1.6% (64) | 1.5% (68) |
| 60-64 | First | 0.6% (161) | 0.1% (1852) | 0.4% (256) | 0.4% (270) |
| | Subsequent | 1.2% (81) | 0.05% (1852) | 3.8% (26) | 3.6% (28) |
| 65-69 | First | 0.8% (119) | 0.2% (463) | 0.6% (171) | 0.6% (180) |
| | Subsequent | 1.7% (60) | 0.2% (412) | 5.6% (18) | 5.3% (19) |
| 70-74 | First | 1.3% (77) | 0.4% (231) | 0.7% (142) | 0.7% (150) |
| | Subsequent | 2.2% (45) | 0.6% (168) | 6.7% (15) | 6.4% (16) |
| 75-79 | First | 1.5% (68) | 1.0% (97) | 1.3% (78) | 1.2% (82) |
| | Subsequent | 2.4% (42) | 1.4% (71) | 9.4% (11) | 9.0% (11) |
| 80-84 | First | 2.1% (49) | 1.9% (52) | 0.9% (111) | 0.9% (118) |
| | Subsequent | 3.2% (31) | 2.5% (40) | 7.4% (13) | 7.1% (14) |
| 85-89 | First | 2.7% (37) | 4.5% (22) | 1.0% (103) | 0.9% (108) |
| | Subsequent | 3.7% (27) | 5.4% (18) | 8.2% (12) | 7.7% (13) |
| 90+ | First | 7.0% (14) | 5.6% (18) | 1.8% (55) | 1.7% (58) |
| | Subsequent | 7.5% (13) | 6.2% (16) | 10.9% (9) | 10.3% (10) |

Age-specific absolute risk reduction (ARR)=(1- relative risk after risedronate)* age-specific risk retrieved from Appendix 3 (Doherty 2001)
Number needed to treat= 1/ARR

**Table 5. Relative risk of minor outcomes after risedronate versus placebo**

| Safety Outcomes | Primary / Secondary Prevention | # of Studies | # of Participants (risedronate / placebo) | Relative Risk (95% CI) | Association P value | Heterogeneity P value |
|---|---|---|---|---|---|---|
| **Risedronate 5 mg/day versus placebo** | | | | | | |

**Table 5. Relative risk of minor outcomes after risedronate versus placebo** *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| Radiographic vertebral | Primary | 2 | 166 / 161 | 0.97 (0.42, 2.25) | 0.94 | NA |
| | Secondary | 3 | 1152 / 1149 | ***0.61 (0.50, 0.75)*** | < 0.00001 | 0.89 |
| Gastrointestinal adverse events | Primary | 2 | 244 / 180 | 0.97 (0.66, 1.44) | 0.89 | 0.20 |
| | Secondary | 6 | 4754 / 4680 | 1.01 (0.93, 1.08) | 0.88 | 0.66 |
| Atypical femoral fracture | Primary | 1 | 115 / 55 | NE | NA | NA |
| | Secondary | 2 | 697 / 686 | NE | NA | NA |
| **Risedronate 2.5 mg/day versus placebo** | | | | | | |
| Radiographic vertebral | Primary | 1 | 127/ 125 | 1.08 (0.48, 2.46) | 0.85 | NA |
| | Secondary | 3 | 926/1068 | ***0.63 (0.45,0.87)*** | 0.005 | 0.48 |
| Gastrointestinal adverse events | Primary | 1 | 127 / 125 | 1.28 (0.75, 2.17) | 0.36 | NA |
| | Secondary | 2 | 3501 / 3543 | 1.01 (0.92, 1.10) | 0.88 | 0.36 |

CI=Confidence Interval; NA=;Not available; NE=Not estimable.

**Table 6. Relative risk of major outcomes after risedronate 2.5 mg/day versus placebo**

| Fracture sites | Primary / Secondary Prevention | # of Studies | # of Participants (risedronate / placebo) | Relative Risk (95% CI) | Association P value | Heterogeneity P value |
|---|---|---|---|---|---|---|
| Non-vertebral | Primary | 1 | 127 / 125 | 0.49 (0.13,1.92) | 0.31 | NA |
| | Secondary | 3 | 1139 / 1242 | 0.80 (0.55,1.16) | 0.24 | 0.76 |
| Withdrawals due to adverse events | Primary | 1 | 127 / 125 | 1.48 (0.62,3.49) | 0.37 | NA |
| | Secondary | 3 | 4332 / 4378 | ***0.89 (0.81,0.98)**** | 0.01 | 0.001 |
| Serious adverse events | Primary | 1 | 127 / 125 | 0.58 (0.31,1.10) | 0.10 | NA |

**Table 6. Relative risk of major outcomes after risedronate 2.5 mg/day versus placebo** *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| | Secondary | 3 | 3521 / 3563 | 0.98 (0.91,1.05) | 0.51 | 51 |

CI=Confidence Interval; NA=Not applicable; NE=Not estimable.
* $I^2$= 85 % and non-significant test for heterogeneity P value= 0.001; Relative Risk 0.90 (95% CI 0.76,1.05) estimated by random-effects model.

**Table 7. Relative risk of fracture after risedronate 5 mg/day: Subgroup analyses**

| Fracture Site | Primary/ Secondary Prevention | Base case | Treatment years | | | Prior bisphosphonate experience |
|---|---|---|---|---|---|---|
| | | | Year 1 | Year 2 | Year 3 | Bisphosphonate-naive |
| Clinical vertebral | Primary | 1/170<br>NE | 1/170<br>NE | 1/170<br>NE | NA | NA |
| | Secondary | 2/119<br>NE | 2/119<br>NE | NA | NA | 1/54<br>NE |
| Non-vertebral | Primary | 3/497<br>0.54 (0.22, 1.35) | 1 / 73<br>0.14 (0.01, 2.60) | 2/424<br>0.71 (0.26, 1.90) | NA | 1/254<br>0.81 (0.25, 2.58) |
| | Secondary | 6/12,173<br>***0.80 (0.72, 0.90)*** | 4/2559<br>0.76 (0.49,1.20) | 3/2724<br>***0.67 (0.49, 0.91)*** | 3/11,770<br>***0.81 (0.72, 0.91)*** | 2/866<br>0.71 (0.47, 1.06) |
| Hip | Primary | 2/243<br>NE | 2/243<br>NE | 1/170<br>NE | NA | NA |
| | Secondary | 3/9450<br>***0.73 (0.56, 0.94)*** | 2/119<br>NE | NA | 1/9331<br>***0.73 (0.56, 0.94)*** | 1/54<br>NE |
| Wrist | Primary | 2/243<br>0.48 (0.03, 7.50) | 1 / 73<br>NE | 1/170<br>0.48 (0.03,7.50) | NA | NA |
| | Secondary | 3/1746<br>0.64 (0.33, 1.24) | 2/119<br>NE | NA | 1/1627<br>0.64 (0.33, 1.23) | 1/54<br>NE |
| Radiographic vertebral | Primary | 2/327<br>0.97 (0.42, 2.25) | 1/73<br>NE | 1/254<br>0.97 (0.42, 2.25) | NA | 1/254<br>0.97 (0.42, 2.25) |
| | Secondary | 3/2301<br>***0.61 (0.50, 0.75)*** | 2/1996 | 3/2152 | 2/2064 | 1/690<br>***0.60 (0.44, 0.81)*** |

**Table 7. Relative risk of fracture after risedronate 5 mg/day: Subgroup analyses** *(Continued)*

| | | | |
|---|---|---|---|
| | ***0.40 (0.27, 0.59)*** | ***0.48 (0.36, 0.64)*** | ***0.62 (0.50, 0.77)*** |

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

**Table 8. Relative risk of fractures after risedronate 2.5 mg/day: Subgroup and Sensitivity analyses**

| Fracture Site | Primary/ Secondary Prevention | Base case | Subgroup analyses | | | Sensitivity analyses with | |
|---|---|---|---|---|---|---|---|
| | | | Year 1 | Year 2 | Bisphosphonate -naive | Baseline denominators | Studies taking fractures as efficacy outcomes |
| Non -vertebral | Primary | 1/252<br>0.49 (0.13, 1.92) | NA | 1/252<br>0.49 (0.13, 1.92) | 1/252<br>0.49 (0.13, 1.92) | 1/254<br>0.49 (0.13, 1.93) | NA |
| | Secondary | 3/2381<br>0.80 (0.55, 1.16) | 2/2361<br>0.87 (0.56, 1.36) | 2/755<br>0.73 (0.44, 1.22) | 1/531<br>0.88 (0.50, 1.53) | 3/2819<br>0.72 (0.52, 1.01) | 2/2157<br>0.81 (0.54, 1.20) |
| Radiographic vertebral | Primary | 1/252<br>1.08 (0.48, 2.46) | NA | 1/252<br>1.08 (0.48, 2.46) | 1/252<br>1.08 (0.48, 2.46) | 1/254<br>1.08 (0.48, 2.46) | NA |
| | Secondary | 3/1994<br>***0.63 (0.45, 0.87)*** | 2/1941<br>***0.56 (0.40, 0.79)*** | 2/716<br>0.66 (0.43, 1.01) | 1/531<br>***0.57 (0.34, 0.95)*** | 3/2819<br>***0.55 (0.41, 0.74)*** | 2/1809<br>***0.58 (0.41-0.82)*** |

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

**Table 9. Relative risk of fracture after risedronate 5 mg/day: Sensitivity analyses**

| Fracture Site | Primary/ Secondary Prevention | Base case | Sensitivity analyses with | | |
|---|---|---|---|---|---|
| | | | Baseline denominators | Studies taking fractures as efficacy outcomes | Excluding McClung 2001 |
| Clinical vertebral | Primary | 1/170<br>NE | 1/171<br>NE | NA | 1/170<br>NE |
| | Secondary | 2/119<br>NE | 2/125<br>NE | NA | 2/119<br>NE |
| Non -vertebral | Primary | 3/497<br>0.54 (0.22, 1.35) | 3/499<br>0.55 (0.22, 1.37) | NA | 3/497<br>0.54 (0.22, 1.35) |
| | Secondary | 6/12,173<br>***0.80 (0.72, 0.90)*** | 6/12,272<br>***0.80 (0.72, 0.90)*** | 3/11,770<br>***0.81 (0.72, 0.91)*** | 5/2842<br>***0.66 (0.50, 0.87)*** |
| Hip | Primary | 2/243<br>NE | 2/244<br>NE | NA | 2/243<br>NE |
| | Secondary | 3/9450<br>***0.73 (0.56, 0.94)*** | 3/9456<br>***0.73 (0.56, 0.94)*** | 1/9331<br>***0.73 (0.56, 0.94)*** | 2/119<br>NE |
| Wrist | Primary | 2/243<br>0.48 (0.03, 7.50) | 2/44<br>0.50 (0.03, 7.85) | NA | 2/243<br>0.48 (0.03, 7.50) |
| | Secondary | 3/1746<br>0.64 (0.33, 1.24) | 3/1766<br>0.64 (0.33, 1.23) | 1/1627<br>0.64 (0.33, 1.24) | 3/1746<br>0.64 (0.33, 1.24) |
| Radiographic vertebral | Primary | 2/327<br>0.97 (0.42, 2.25) | 2/328<br>0.98 (0.42, 2.27) | NA | 2/327<br>0.97 (0.42, 2.25) |
| | Secondary | 3/2301<br>***0.61 (0.50, 0.75)*** | 3/2816<br>***0.61 (0.50, 0.76)*** | 2/2064<br>***0.62 (0.50, 0.77)*** | 3/2301<br>***0.61 (0.50, 0.75)*** |

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

# APPENDICES

## Appendix 1. Search Strategies for Risedronate Updated Review, 2012, 2019 and 2021

### 1-1 Search Strategies in June 2012

| Database, and coverage | Search date | Number of references retrieved | Number of references after de-duplication |
|---|---|---|---|
| Ovid MEDLINE(R) 1946-2012 | 28 June 2012 | 657 | 124 |
| Embase Classic+Embase 1947-2012 | 28 June 2012 | 172 | 189 |
| Cochrane Library Issue 6 2012 | 28 June 2012 | 3 | 3 |
| Cochrane Reviews | | 5 | 5 |
| DARE | | 11 | 11 |
| Economic Evaluations | | 4 | 4 |
| Technology Assessments | | 3 | 0 |
| Methods Studies | | 178 | 177 |
| Trials | | | |
| **Totals** | | **1033** | **513** |

**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. Risedronate.tw.

18. risedronic acid.tw.

19. Acrel.tw.

20. Actokit.tw.

21. Actonel.tw.

22. Aventis.tw.

23. Alesone.tw.

24. Atelvia.tw.

25. Avestra.tw.

26. Benet.tw.

27. Boneact.tw.

28. Ductonar.tw.

29. Juverital.tw.

30. Miosen.tw.

31. Norifaz.tw.

32. Norsed.tw.

33. Nurrid.tw.

34. Optinate.tw.

35. Osteonate.tw.

36. Racidrix.tw.

37. Rentop.tw.

38. Retonel.tw.

39. Ribastamin.tw.

40. Ridron.tw.

41. Risedon.tw.

42. Risedross.tw.

43. Risemyl.tw.

44. Risendros.tw.

45. Riseos.tw.

46. Riseratio.tw.

47. Risofos.tw.

48. Risonate.tw.

49. Rizat.tw.

50. Seralis.tw.

51. Tevanel.tw.

52. Vionate.tw.

53. or/16-51

54. 15 and 53

55. randomized controlled trial.pt.

56. controlled clinical trial.pt.

57. randomized.ab.

58. placebo.ab.

59. drug therapy.fs.

60. randomly.ab.

61. trial.ab.

62. groups.ab.

63. or/55-62

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

65. 63 not 64

66. 54 and 65

**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. risedronic acid/

16. Risedronate.tw.

17. risedronic acid.tw.

18. Acrel.tw.

19. Actokit.tw.

20. Actonel.tw.

21. Aventis.tw.

22. Alesone.tw.

23. Atelvia.tw.

24. Avestra.tw.

25. Benet.tw.

26. Boneact.tw.

27. Ductonar.tw.

28. Juverital.tw.

29. Miosen.tw.

30. Norifaz.tw.

31. Norsed.tw.

32. Nurrid.tw.

33. Optinate.tw.

34. Osteonate.tw.

35. Racidrix.tw.

36. Rentop.tw.

37. Retonel.tw.

38. Ribastamin.tw.

39. Ridron.tw.

40. Risedon.tw.

41. Risedross.tw.

42. Risemyl.tw.

43. Risendros.tw.

44. Riseos.tw.

45. Riseratio.tw.

46. Risofos.tw.

47. Risonate.tw.

48. Rizat.tw.

49. Seralis.tw.

50. Tevanel.tw.

51. Vionate.tw.

52. or/15-51

53. 14 and 52

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

55. RETRACTED ARTICLE/

56. 54 or 55

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

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

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

60. 56 not (57 or 58 or 59)

61. 53 and 60

**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 Risedronate:ti,ab

#18 risedronic next acid:ti,ab

#19 Acrel:ti,ab

#20 Actokit:ti,ab

#21 Actonel:ti,ab

#22 Aventis:ti,ab

#23 Alesone:tio,ab

#24 Atelvia:ti,ab

#25 Avestra:ti,ab

#26 Benet:ti,ab

#27 Boneact:ti,ab

#28 Ductonar:ti,ab

#29 Juverital:ti,ab

#30 Miosen:ti,ab

#31 Norifaz:ti,ab

#32 Norsed:ti,ab

#33 Nurrid:ti,ab

#34 Optinate:ti,ab

#35 Osteonate:ti,ab

#36 Racidrix:ti,ab

#37 Rentop:ti,ab

#38 Retonel:ti,ab

#39 Ribastamin:ti,ab

#40 Ridron:ti,ab

#41 Risedon:ti,ab

#42 Risedross:ti,ab

#43 Risemyl:ti,ab

#44 Risendros:ti,ab

#45 Riseos:ti,ab

#46 Riseratio:ti,ab

#47 Risofos:ti,ab

#48 Risonate:ti,ab

#49 Rizat:ti,ab

#50 Seralis:ti,ab

#51 Tevanel:ti,ab

#52 Vionate:ti,ab

#53 (#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)

#54 (#15 AND #53)

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**1-2 Search Strategies in June 2019**

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 Risedronate Sodium/ (8732)

29 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).tw,kw,rn. (22128)

30 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).tw,kw,rn. (79)

31 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).tw,kw,rn. (4672)

32 or/28-31 [RISEDRONATE] (26784)

33 27 and 32 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3350)

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 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1313)

42 Male/ not (Female/ and Male/) (5515219)

43 41 not 42 [MALE-ONLY REMOVED] (1297)

44 exp Animals/ not (exp Animals/ and Humans/) (18276792)

45 43 not 44 [ANIMAL-ONLY REMOVED] (1007)

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] (997)

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 risedronic acid/ (8902)

80 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).tw,kw,rn. (22128)

81 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).tw,kw,rn. (79)

82 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).tw,kw,rn. (4672)

83 or/79-82 [RISEDRONATE] (26786)

84 78 and 83 [RISEDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3598)

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 [RISEDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1384)

93 male/ not (female/ and male/) (5515219)

94 92 not 93 [MALE-ONLY REMOVED] (1368)

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] (1358)

99 editorial.pt. (1096605)

100 letter.pt. not (letter.pt. and randomized controlled trial/) (2094824)

101 98 not (99 or 100) [OPINION PIECES REMOVED] (1343)

102 (2017082* or 201709* or 201710* or 201711* or 201712* or 2018* or 2019*).dc. (3221271)

103 101 and 102 (62)

104 103 use emczd [EMBASE RECORDS] (62)

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*).ti,ab,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*).ti,ab,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 Risedronate Sodium/ (8732)

133 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).ti,ab,kw. (7289)

134 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).ti,ab,kw. (46)

135 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).ti,ab,kw. (2106)

136 or/132-135 [RISEDRONATE] (14567)

137 131 and 136 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3339)

138 Male/ not (Female/ and Male/) (5515219)

139 137 not 138 [MALE-ONLY REMOVED] (3304)

140 ("201708" or "201709" or "201710" or "201711" or "201712" or 2018* or 2019*).up. (34609819)

141 139 and 140 (1210)

142 141 use cctr [CENTRAL RECORDS] (309)

143 51 or 104 or 142 [ALL DATABASES] (383)

144 remove duplicates from 143 (353) [TOTAL UNIQUE RECORDS]

145 144 use medall [MEDLINE UNIQUE RECORDS] (12)

146 144 use emczd [[EMBASE UNIQUE RECORDS] (50)

147 144 use cctr [CENTRAL UNIQUE RECORDS] (291)

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**1-3 Search Strategies in March 2021**

Database: Embase Classic+Embase <1947 to 2021 March 23> , Ovid MEDLINE(R) ALL <1946 to March 23, 2021>, EBM Reviews - Cochrane Central Register of Controlled Trials <February 2021>

*Updated from 2019 Jun 5*

Search Strategy:

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1 Osteoporosis, Postmenopausal/ (21102)

2 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (26946)

3 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4554)

4 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (234)

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. (6115)

8 (bone loss* adj5 menopaus*).tw,kw. (1751)

9 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (496)

10 (osteoporo* adj5 age-related).tw,kw. (1422)

11 (bone loss* adj5 age-related).tw,kw. (1925)

12 (osteoporo* adj5 senil*).tw,kw. (2007)

13 (bone loss* adj5 senil*).tw,kw. (60)

14 or/1-13 (49178)

15 Osteoporosis/ (174060)

16 osteoporo*.tw,kw. (225901)

17 Bone Density/ (158247)

18 (bone? adj3 densit*).tw,kw. (153965)

19 bmd.tw,kw. (89288)

20 bone loss*.tw,kw. (76265)

21 or/15-20 (424295)

22 Menopause/ (82262)

23 Postmenopause/ (99150)

24 (postmenopaus* or post-menopaus*).tw,kw. (180141)

25 or/22-24 (253384)

26 21 and 25 (64497)

27 14 or 26 [POST-MENOPAUSAL OSTEOPOROSIS] (77442)

28 Risedronate Sodium/ (9298)

29 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).tw,kw,rn. (23587)

30 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).tw,kw,rn. (81)

31 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).tw,kw,rn. (5274)

32 or/28-31 [RISEDRONATE] (28848)

33 27 and 32 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3567)

34 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (1217390)

35 clinical trials as topic.sh. (228475)

36 exp Randomized Controlled Trials as Topic/ (353435)

37 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (3696719)

38 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (750685)

39 trial.ti. (914658)

40 or/34-39 (4564783)

41 33 and 40 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (1419)

42 Male/ not (Female/ and Male/) (5974590)

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

44 exp Animals/ not (exp Animals/ and Humans/) (19236845)

45 43 not 44 [ANIMAL-ONLY REMOVED] (1113)

46 (comment or editorial or interview or news or newspaper article).pt. (2215277)

47 (letter not (letter and randomized controlled trial)).pt. (2296752)

48 45 not (46 or 47) [OPINION PIECES REMOVED] (1102)

49 (201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).dt. (2587003)

50 48 and 49 (16)

51 50 use medall [MEDLINE RECORDS] (16)

52 postmenopause osteoporosis/ (14690)

53 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (26946)

54 (bone loss* adj5 (postmenopaus* or post-menopaus*)).tw,kw. (4554)

55 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).tw,kw. (234)

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. (6115)

59 (bone loss* adj5 menopaus*).tw,kw. (1751)

60 (bone loss* adj5 "after" adj5 menopaus*).tw,kw. (496)

61 (osteoporo* adj5 age-related).tw,kw. (1422)

62 (bone loss* adj5 age-related).tw,kw. (1925)

63 (osteoporo* adj5 senil*).tw,kw. (2007)

64 (bone loss* adj5 senil*).tw,kw. (60)

65 or/52-64 (44271)

66 osteoporosis/ (174060)

67 osteoporo*.tw,kw. (225901)

68 bone density/ (158247)

69 (bone? adj3 densit*).tw,kw. (153965)

70 bmd.tw,kw. (89288)

71 bone loss*.tw,kw. (76265)

72 or/66-71 (424295)

73 menopause/ (82262)

74 postmenopause/ (99150)

75 (postmenopaus* or post-menopaus*).tw,kw. (180141)

76 or/73-75 (253384)

77 72 and 76 (64497)

78 65 or 77 [POST-MENOPAUSAL OSTEOPOROSIS] (74515)

79 risedronic acid/ (9468)

80 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).tw,kw,rn. (23587)

81 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).tw,kw,rn. (81)

82 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).tw,kw,rn. (5274)

83 or/79-82 [RISEDRONATE] (28850)

84 78 and 83 [RISEDRONATE - POST-MENOPAUSAL OSTEOPOROSIS] (3801)

85 randomized controlled trial/ (1182940)

86 controlled clinical study/ (467749)

87 exp "clinical trial (topic)"/ (352155)

88 (randomi#ed or randomi#ation* or randomly or RCT? or placebo*).tw,kw. (3696719)

89 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (750685)

90 trial.ti. (914658)

91 or/85-90 (4533772)

92 84 and 91 [RISEDRONATE - POST-MENOPAUSAL OSTEOPOROSIS - RCTs] (1491)

93 male/ not (female/ and male/) (5974590)

94 92 not 93 [MALE-ONLY REMOVED] (1475)

95 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (54328116)

96 exp human/ or exp human experimentation/ or exp human experiment/ (43287410)

97 95 not 96 (11042583)

98 94 not 97 [ANIMAL-ONLY REMOVED] (1465)

99 editorial.pt. (1252978)

100 letter.pt. not (letter.pt. and randomized controlled trial/) (2296600)

101 98 not (99 or 100) [OPINION PIECES REMOVED] (1450)

102 (201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).dc. (3831831)

103 101 and 102 (64)

104 103 use emczd [EMBASE RECORDS] (64)

105 Osteoporosis, Postmenopausal/ (21102)

106 (osteoporo* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (26946)

107 (bone loss* adj5 (postmenopaus* or post-menopaus*)).ti,ab,kw. (4554)

108 (osteoporo* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (234)

109 (bone loss* adj5 (perimenopaus* or peri-menopaus*)).ti,ab,kw. (218)

110 (osteoporo* adj5 "after" adj5 menopaus*).ti,ab,kw. (693)

111 (osteoporo* adj5 menopaus*).ti,ab,kw. (6115)

112 (bone loss* adj5 menopaus*).ti,ab,kw. (1751)

113 (bone loss* adj5 "after" adj5 menopaus*).ti,ab,kw. (496)

114 (osteoporo* adj5 age-related).ti,ab,kw. (1422)

115 (bone loss* adj5 age-related).ti,ab,kw. (1925)

116 (osteoporo* adj5 senil*).ti,ab,kw. (2007)

117 (bone loss* adj5 senil*).ti,ab,kw. (60)

118 or/105-117 (49178)

119 Osteoporosis/ (174060)

120 osteoporo*.ti,ab,kw. (225901)

121 Bone Density/ (158247)

122 (bone? adj3 densit*).ti,ab,kw. (153964)

123 bmd.ti,ab,kw. (89272)

124 bone loss*.ti,ab,kw. (76265)

125 or/119-124 (424281)

126 Menopause/ (82262)

127 Postmenopause/ (99150)

128 (postmenopaus* or post-menopaus*).ti,ab,kw. (180141)

129 or/126-128 (253384)

130 125 and 129 (64497)

131 118 or 130 [POST-MENOPAUSAL OSTEOPOROSIS] (77442)

132 Risedronate Sodium/ (9298)

133 (risedronate or risedronic acid or acrel or actokit or actonel or atelvia or aventis or alesone or atelvia or avestra or benet or boneact or ductonar or juverital or miosen).ti,ab,kw. (8128)

134 (ne 58095 or ne58095 or norifaz or norsed or nurrid or optinate or osteonate).ti,ab,kw. (48)

135 (racidrix or rentop or retonel or ribastamin or ridron or risedon or risedross or risemyl or risendros or riseos or riseratio or risofos or resonate or rizat or seralis or tevanel or vionate).ti,ab,kw. (2592)

136 or/132-135 [RISEDRONATE] (16209)

137 131 and 136 [RISEDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS] (3555)

138 Male/ not (Female/ and Male/) (5974590)

139 137 not 138 [MALE-ONLY REMOVED] (3514)

140 (201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020* or 2021*).up. (37492635)

141 139 and 140 (1186)

142 141 use cctr [CENTRAL RECORDS] (240)

143 51 or 104 or 142 [ALL DATABASES] (320)

144 remove duplicates from 143 (292) [TOTAL UNIQUE RECORDS – UPDATE PERIOD]

145 144 use medall [MEDLINE UNIQUE RECORDS] (16)

146 144 use emczd [EMBASE UNIQUE RECORDS] (50)

147 144 use cctr [CENTRAL UNIQUE RECORDS] (226)

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## Appendix 2. Models for fracture risk in postmenopausal women: FRACTURE index

| Questions | | Point Score |
|---|---|---|
| 1. What is your current age? | Less than 65 | 0 |
| | 65–69 | 1 |
| | 70–74 | 2 |
| | 75–79 | 3 |

(Continued)

| | | |
|---|---|---|
| | 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 |

## Appendix 3. 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 |
| 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 |

## Appendix 4. Estimated five year age-specific risks of first and subsequent osteoporotic fractures (From Doherty et al 2001)

| Age (years) | Risk of Fractures (%) | | | | | |
|---|---|---|---|---|---|---|
| | 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 |

*Other: non-vertebral, including wrist, forearm, humerus, tibia/fibula, pelvis, ribs, femur but exclude hip

## Appendix 5. List and management of the reported data (of eligible studies) excluded from the analyses

**Table 1 Reasons and relevant data for four studies excluding from analyses (data not extractable)**

| Study ID: reasons for excluding from analysis | Outcome data related to risedronate |
|---|---|
| Clemmesen 1997 for secondary prevention:<br><br>Reported data covered 1-year follow-up when all participants discontinued medications. | Data not usable.<br><br>Risedronate 2.5 mg/day (44 women) versus Placebo (44 women):<br><br>1. Radiographic vertebral fractures: 13 (29.5%) versus 20 (45.5%)<br><br>2. Non-vertebral fractures: 4 (9.1%) versus 4 (9.1%)<br><br>3. Withdrawals due to adverse events: data (19) not reported by group<br><br>4. Serious adverse events: data were not reported but stated “the most common serious adverse event was bone related to trauma (falls)”.<br><br>5. Gastrointestinal adverse events: 3 (6.8%) versus 3 (6.8%) |
| Kato 2010 for primary prevention:<br><br>An abstract. The numbers of the randomised participants by group were not reported. It only reported “No incidence vertebral fracture of L3 was seen during the study period”. | Data not extractable. |
| Lim 2017, undefined: | Data not extractable. |

*(Continued)*

| | |
|---|---|
| An abstract. Overall clinical fractures were reported but not by anatomic sites and groups. The treatment duration was not reported. | In risedronate, estrogen and control group, new clinical fracture were reported for 15. 6%, 12.8%, and 11. 2% participants, respectively. There were no significant differences in the rate. |
| Narula 2012 for secondary prevention:<br><br>It only stated that "... the most common adverse events reported were upper gastrointestinal complaints like…". No data were reported. | Data not extractable. |

**Table 2 Relative risk of major and minor outcomes after risedronate 5 mg/day versus the therapeutic equivalents***

| Outcomes | Primary / Secondary Prevention | # of Studies | Risedronate dose: number of women events/number of women | | | | Relative Risk (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | 5 mg/day | 35 mg/week | 75 mg*2day/ moth† | 150 mg/ month | |
| Clinical vertebral fractures | Primary | 1 | 0 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 2 | 25 / 787‡ | 27 / 1100‡ | NA | NA | 0.98 (0.58,1.68) |
| | Secondary | 1 | 5 / 613 | NA | 6 / 616 | NA | 0.84 (0.26,2.73) |
| | Secondary | 1 | 6 / 642 | NA | NA | 4 / 650 | 1.52 (0.43,5.76) |
| Non-vertebral fractures | Primary | 1 | 0 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 2 | 57 / 787‡ | 74 / 1100‡ | NA | NA | 0.99 (0.71,1.39) |
| | Secondary | 1 | 31 / 613 | NA | 35 / 616 | NA | 0.89 (0.56,1.42) |
| | Secondary | 1 | 25 / 642 | NA | NA | 28 / 650 | 0.90 (0.53,1.53) |
| Hip fractures | Primary | 1 | 0 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 1 | 2 / 642 | NA | NA | 0 / 650 | 5.06 (0.24,105.24) |
| Wrist fractures | Primary | 1 | 0 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 1 | 1 / 642 | NA | NA | 1 / 650 | 1.01 (0.06,16.15) |
| Withdrawal due to adverse events | Primary | 1 | 8 / 144 | 10 / 145 | NA | NA | 0.81 (0.33,1.98) |
| | Secondary | 2 | 103/787‡ | 137/1100‡ | NA | NA | 0.97 (0.76,1.24) |
| | Secondary | 1 | 86 / 613 | NA | 80 / 616 | NA | 1.08 (0.81,1.43) |
| | Secondary | 1 | 84 / 642 | NA | NA | 88 / 650 | 0.97 (0.73,1.28) |
| Serious | Primary | 1 | 5 / 144 | 7 / 145 | NA | NA | 0.72 (0.23,2.21) |

*(Continued)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| adverse events | Secondary | 2 | 98/787‡ | 128/1100‡ | NA | NA | 1.02 (0.80,1.31) |
| | Secondary | 1 | 66 / 613 | NA | 89 / 616 | NA | 0.75 (0.55,1.00) |
| | Secondary | 1 | 51 / 642 | NA | NA | 77 / 650 | **0.67 (0.48,0.94)** |
| Radiographic vertebral fractures | Primary | 1 | 0 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 2 | 17 / 722‡ | 14 / 1018‡ | NA | NA | 1.62 (0.78,3.35) |
| | Secondary | 1 | 15 / 613 | NA | 16 / 616 | NA | 0.94 (0.47,1.97) |
| | Secondary | 1 | 14 / 560 | NA | NA | 15 / 577 | 0.96 (0.47,1.89) |
| Gastrointestinal adverse events | Primary | 1 | 17 / 144 | 18 / 145 | NA | NA | 0.95 (0.51,1.77) |
| | Secondary | 2 | 165/787‡ | 252/1100‡ | NA | NA | 0.88 (0.74,1.05) |
| | Secondary | 1 | 169/613 | NA | 162 / 616 | NA | 1.05 (0.87,1.26) |
| | Secondary | 1 | 148/642 | NA | NA | 169 / 650 | 0.89 (0.73,1.07) |
| Atypical femoral fracture | Primary | 1 | 0 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 1 | 0 / 613 | NA | 0 / 616 | NA | NE |
| Acute phase reaction | Secondary | 1 | 4 / 307 | 11 / 615 | NA | NA | 0.73 (0.23,2.27) |
| | Secondary | 1 | 0 / 613 | NA | 4 / 616 | NA | 0.11 (0.01,2.07) |
| | Secondary | 1 | 1 / 642 | NA | NA | 9 / 650 | ***0.11 (0.01,0.89)*** |
| Atrial fibrillation | Secondary | 1 | 0 / 307‡ | 2 / 615‡ | NA | NA | 0.40 (0.02,8.31) |
| | Secondary | 1 | 4 / 642 | NA | NA | 7 / 650 | 0.58 (0.17,1.97) |
| Osteonecrosis of the jaw | Primary | 1 | 1 / 144 | 0 / 145 | NA | NA | NE |
| | Secondary | 1 | 0 / 307‡ | 0 / 615‡ | NA | NA | NE |
| | Secondary | 1 | 0 / 613 | NA | 0 / 616 | NA | NE |

| | | | | | |
|---|---|---|---|---|---|
| Secondary | 1 | 0 / 642 | NA | NA | 0 / 650 | NE |

(Continued)

* One primary (Gu 2015) and four secondary prevention studies (Brown 2002; Delmas 2008a; Delmas 2008b; McClung 2012) compared benefit and harm outcomes of risedronate at therapeutic equivalent doses.

† Risedronate 75 mg on two consecutive days each month (Delmas 2008b).

‡ The two delayed-release arms (DR), risedronate 35 mg/week taken at least 30 minutes before breakfast and 35 mg/week taken immediately following breakfast were combined, and compared with risedronate 5 mg/day (McClung 2012).

CI = Confidence Interval; NA = Not applicable; NE = Not estimable.

**Table 3 Relative risk of major and minor outcomes for pairwise comparison of risedronate at unapproved dose regimen***

| Major outcomes | comparisons | # of Studies | number of women events/ number of women | | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | | | Intervention | comparator | |
| **Clinical vertebral fractures** | **Secondary prevention** | | | | |
| | Risedronate 35 mg/wee‡ vs Risedronate 50 mg/week | 1 | 48 / 965 | 22 / 491 | 1.11 (0.68,1.82) |
| | Risedronate 2.5 mg/day vs Risedronate 25 mg/month | 1 | 1 / 199 | 1 / 340 | 1.71 (0.11,27.16) |
| | Risedronate 2.5 mg/day vs Risedronate 37.5 mg/month | 1 | 1/ 199 | 5 / 331 | 1.66 (0.10,26.44) |
| **Non-vertebral fractures** | **Primary prevention** | | | | |
| | Risedronate 5 mg/day vs Risedronate 5 mg/day, cyclic† | 1 | 0 / 37 | 1 / 38 | 0.34 (0.01,8.14) |
| | **Secondary prevention** | | | | |
| | Risedronate 35 mg/week‡ vs Risedronate 50 mg/week | 1 | 83 / 965 | 38 / 491 | 1.11 (0.77,1.61) |
| **Hip fractures** | **Primary prevention** | | | | |
| | Risedronate 5 mg/day vs Risedronate 5 mg/day, cyclic | 1 | 0 / 37 | 0 / 38 | NE |
| **Wrist fractures** | **Primary prevention** | | | | |
| | Risedronate 5 mg/day vs Risedronate 5 mg/day, cyclic† | 1 | 0 / 37 | 1 / 38 | 0.34 (0.01,8.14) |
| **Withdrawal due to adverse events** | **Secondary prevention** | | | | |
| | Risedronate 35 mg/week‡ vs Risedronate 50 mg/week | 1 | 150 / 965 | 60 / 491 | 1.27 (0.96,1.68) |
| | Risedronate 2.5 mg/day vs Risedronate 25 mg/month | 1 | 13 / 199 | 31 / 340 | 0.72 (0.38,1.34) |

*(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | Risedronate 2.5 mg/day vs Risedronate 37.5 mg/month | 1 | 13/ 199 | 29 / 332 | 0.75 (0.40,1.40) |
| **Serious adverse events** | **Secondary prevention** | | | | |
| | Risedronate 35 mg/week‡ vs Risedronate 50 mg/week | 1 | 131 / 965 | 79 / 491 | 0.84 (0.65,1.09) |
| | Risedronate 2.5 mg/day vs Risedronate 25 mg/month | 1 | 12 / 199 | 23 / 340 | 0.89 (0.45,1.75) |
| | Risedronate 2.5 mg/day vs Risedronate 37.5 mg/month | 1 | 12/ 199 | 13/ 331 | 1.54 (0.71,3.30) |
| **Radiographic vertebral fractures** | **Primary prevention** | | | | |
| | Risedronate 5 mg/day vs Risedronate 5 mg/day, cyclic† | 1 | 0 / 37 | 1 / 38 | 0.34 (0.01,8.14) |
| | **Secondary prevention** | | | | |
| | Risedronate 35 mg/week‡ vs Risedronate 50 mg/week | 1 | 18 / 818 | 7 / 422 | 1.33 (0.56,3.15) |
| | Risedronate 2.5 mg/day vs Risedronate 25 mg/month | 1 | 4 / 190 | 8 / 316 | 0.83 (0.25,2.72) |
| | Risedronate 2.5 mg/day vs Risedronate 37.5 mg/month | 1 | 4 / 190 | 5 / 300 | 1.26 (0.34,4.64) |
| **Gastrointestinal adverse events** | **Secondary prevention** | | | | |
| | Risedronate 35 mg/week‡ vs Risedronate 50 mg/week | 1 | 233 / 965 | 122 / 491 | 0.97 (0.80,1.18) |

* One primary (Mortensen 1998) and two secondary prevention studies (Brown 2002; NCT02063854) compared benefit and harm outcomes of risedronate at approved versus unapproved dose regimen.

† Risedronate 5 mg daily for the first 2 weeks of every calendar month and placebo daily for the rest of the month (Mortensen 1998).

‡ Arm of risedronate 35 mg/week and risedronate 5 mg/day were combined and compared with risedronate 50 mg/week (Brown 2002).

## Appendix 6. Relative risk of major and minor outcomes after risedronate 5 mg/day versus 2.5 mg/day

| Outcomes | Primary / Secondary Prevention | # of Studies | # of Participants (daily risedronate 5/2.5 mg) | Relative Risk (95% CI) | Association P value | Heterogeneity P value |
|---|---|---|---|---|---|---|
| Non-vertebral fracture | Primary | 1 | 129/127 | 1.64 (0.40,6.72) | 0.49 | NA |

*(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| | Secondary | 3 | 1256/1139 | 0.85 (0.57,1.29) | 0.45 | 0.90 |
| Withdrawal due to adverse events | Primary | 1 | 129/127 | 0.57 (0.23, 1.41) | 0.23 | NA |
| | Secondary | 3 | 4324/4312 | 1.09 (0.99, 1.20)* | 0.08 | 0.005 |
| Serious adverse events | Primary | 1 | 129/127 | 0.91 (0.43, 1.91) | 0.80 | NA |
| | Secondary | 2 | 3512 / 3501 | 1.02 (0.95, 1.09)† | 0.59 | 0.05 |
| Radiographic vertebral fracture | Primary | 1 | 129/127 | 0.89 (0.39, 2.03) | 0.79 | NA |
| | Secondary | 3 | 1084/926 | ***0.66 (0.44,0.98)*** | 0.04 | 0.85 |
| Gastrointestinal adverse events | Primary | 1 | 129/127 | 0.95 (0.58, 1.55) | 0.83 | NA |
| | Secondary | 2 | 3512 / 3501 | 0.97 (0.89, 1.06) | 0.56 | 0.13 |

CI=Confidence Interval; NA=Not available; NE=Not estimable.

* $I^2$=81 % and non-significant test for heterogeneity P value=0.005. Relative Risk 1.22 (95% CI 0.91,1.64) estimated by random-effects model.

† $I^2$=73 % and non-significant test for heterogeneity P value = 0.05. Relative Risk 1.08 (95% CI 0.89,1.31) estimated by random-effects model.

## Appendix 7. Weighted relative risk of benefit and harm after risedronate versus active drug, secondary prevention

**Table 1 Weighted relative risk of major outcomes after risedronate versus active drug, secondary prevention**

| Major outcomes | comparisons | # of Studies | number of women events/number of women | | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | | | Intervention | comparator | |
| Clinical vertebral fracture | Risedronate 35 mg/week versus Alendronate 70 mg/week | 3 | 0 / 142 | 0 / 250 | NE |
| | | | - 0 / 52 | - 0 / 60 | |
| | | | - 0 / 32 | - 0 / 133 | |
| | | | - 0 / 58 | - 0 / 57 | |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 2 | 0 / 90 | 0 / 90 | NE |

*(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | | | - 0 / 32 | - 0 / 33 | |
| | | | - 0 / 58 | - 0 / 57 | |
| | Risedronate 150 mg/month versus Denosumab 60 mg/6 months, sc | 1 | 0 / 429 | 1 / 429 | 0.33 (0.01,8.16) |
| Non-vertebral | Risedronate 35 mg/week versus Alendronate 70 mg/week | 3 | 0 / 109 | 0 / 218 | NE |
| | | | - 0 / 52 | - 0 / 60 | |
| | | | - 0 / 25† | - 0 / 25† | |
| | | | - 0 / 32 | - 0 / 133 | |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 1 | 0 / 32 | 0 / 33 | NE |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 2 | 67 / 1030 | 53 / 1040 | 1.28 (0.90,1.82) |
| | | | - 29 / 350 | - 28 / 360 | |
| | | | - 38 / 680 | - 25 / 680 | |
| | Risedronate 2.5 mg/day versus Etidronate 200 mg/day | 1 | 7 / 118 | 4 / 117 | 1.74 (0.52,5.77) |
| | Risedronate 17.5 mg/week versus (Risedronate 17.5 mg/week + Menatetrenone 45 mg/day | 1 | 24 / 943* | 20 / 931* | 1.88 (0.66,2.13) |
| Hip fracture | Risedronate 35 mg/week versus Alendronate 70 mg/week | 4 | 0 / 167 | 0 / 275 | NE |
| | | | - 0 / 52 | - 0 / 60 | |
| | | | - 0 / 25† | - 0 / 25† | |
| | | | - 0 / 32 | - 0 / 133 | |
| | | | - 0 / 58 | - 0 / 57 | |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 2 | 0 / 90 | 0 / 90 | NE |
| | | | - 0 / 32 | - 0 / 33 | |
| | | | - 0 / 58 | - 0 / 57 | |
| | Risedronate 150 mg/month versus Denosumab 60 mg/6 months, sc | 1 | 1 / 429 | 1 / 429 | 1.00 (0.06,15.94) |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 2 | 7 / 1030 | 7 / 1040 | 1.01 (0.36,2.89) |
| | | | - 2 / 350 | - 5 / 360 | |
| | | | - 5 / 680 | - 2 / 680 | |

*(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | Risedronate 17.5 mg/week versus (Risedronate 17.5 mg/week + Menatetrenone 45 mg/day) | 1 | 0 / 943* | 0 / 931* | NE |
| Wrist fracture | Risedronate 35 mg/week versus Alendronate 70 mg/week | 3 | 0 / 109 | 0 / 218 | NE |
| | | | - 0 / 52 | - 0 / 60 | |
| | | | - 0 / 25† | - 0 / 25† | |
| | | | - 0 / 32 | - 0 / 133 | |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 1 | 0 / 32 | 0 / 33 | NE |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 2 | 3 / 1033 | 5 / 1043 | 0.61 (0.15,2.56) |
| | | | - 2 / 350 | - 4 / 360 | |
| | | | - 1 / 683 | - 1 / 683 | |
| | Risedronate 17.5 mg/week versus (Risedronate 17.5 mg/week + Menatetrenone 45 mg/day) | 1 | 0 / 943* | 1 / 931* | 0.33(0.01,8.07) |
| Withdrawals due to adverse events | Risedronate 35 mg/week versus Alendronate 70 mg/week | 4 | 66 / 725 | 57 / 723 | 1.15 (0.82, 1.61) |
| | | | - 0 / 14‡ | - 0 / 16‡ | |
| | | | - 34 / 468 | - 24 / 468 | |
| | | | - 1 / 21‡ | - 2 / 20‡ | |
| | | | - 31 / 222† | - 31 / 219† | |
| | Risedronate 150 mg/month versus Denosumab 60 mg/6 months, sc | 1 | 13 / 429 | 3 / 429 | 4.33 (1.24, 15.10) |
| | Risedronate 35 mg/week versus Parathyroid hormone 100 µg/day, sc | 1 | 3 / 132 | 13 / 136 | ***0.24 (0.07, 0.82)*** |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 3 | 77 / 1055 | 101 / 1065 | 0.77 (0.58, 1.02) |
| | | | - 0 / 22 | - 0 / 22 | |
| | | | - 23 / 350 | - 31 / 360 | |
| | | | - 54 / 683 | - 70 / 683 | |
| | Risedronate 2.5 mg/day versus Etidronate 200 mg/day | 1 | 8 / 118 | 7 / 117 | 1.13 (0.42, 3.02) |
| | Risedronate 2.5 mg/day versus Teriparatide 20 µg/day, sc | 1 | 0 / 20 | 0 / 20 | NE |

*(Continued)*

| | | | | | |
|---|---|---|---|---|---|
| | Risedronate 17.5 mg/week versus<br>(Risedronate 17.5 mg/week+ Menatetrenone 45 mg/day) | 2 | 29 / 993<br>- 11 / 50<br>- 18 / 943* | 46 / 982<br>- 15 / 51<br>- 31 / 931* | ***0.63***<br>***(041, 0.98)*** |
| Serious adverse events | Risedronate 35 mg/week versus Risedronate 50 mg/week | 1 | 131 / 965 | 79 / 491 | 0.84<br>(0.65,1.09) |
| | Risedronate 35 mg/week versus Alendronate 70 mg/week | 5 | 67 / 733<br>- 0 / 14‡<br>- 44 / 395<br>- 15 / 222†<br>- 8 / 58<br>- 0 / 44 | 61 / 742<br>- 0 / 16‡<br>- 42 / 403<br>- 17 / 219†<br>- 2 / 57<br>- 0 / 47 | 1.11<br>(0.80, 1.54) |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 1 | 8 / 58 | 7 / 57 | 1.12<br>(0.44, 2.89) |
| | Risedronate 150 mg/month versus Denosumab 60 mg/6 months, sc | 1 | 35 / 429 | 33 / 429 | 1.06<br>(0.67, 1.67) |
| | Risedronate 35 mg/week versus Raloxifene 60 mg/day | 1 | 0 / 44 | 0 / 36 | NE |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 3 | 180 / 1052<br>- 0 / 22<br>- 65 / 350<br>- 115 / 680 | 192 / 1062<br>- 0 / 22<br>- 55 / 360<br>- 137 / 680 | 0.95<br>(0.79, 1.14) |
| | Risedronate 2.5 mg/day versus Teriparatide 20 µg/day, sc | 1 | 0 / 20 | 0 / 20 | NE |
| | Risedronate 17.5 mg/week versus (Risedronate 17.5 mg/week + Menatertrenone 45 mg/d) | 1 | 16 / 943* | 13 / 931* | 1.13<br>(0.55, 2.30) |

* In Tanaka 2017, risedronate 2.5 mg/day or 17.5 mg/week was used in two arms.

† In Sarioglu 2006 and Hosking 2003, risedronate 5 mg/day was compared with alendronate 70 mg/week.

‡ In Atmaca 2006 and Dobnig 2006, risedronate 5 mg/day was compared with alendronate 10 mg/day.

IM = intramuscular injection; IV = intravenous injection; sc: subcutaneous injection.

**Table 2 Weighted relative risk of minor outcomes after risedronate versus active drug, secondary prevention**

| Minor outcomes | Comparison | # of Studies | number of women with events/number of women | | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | | | **Intervention** versus**comparator** | | |
| Radiographic vertebral fractures | Risedronate 5 mg/day versus Alendronate 70 mg/week | 1 | 0 / 25 | 0 / 25 | NE |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 2 | 97 / 842 | 44 / 833 | 2.18 (1.55,3.07) |
| | | | - 33 / 309 | - 16 / 317 | |
| | | | - 64 / 533 | - 28 / 516 | |
| | Risedronate 2.5 mg/day versus Etidronate 200 mg/day | 1 | 0 / 101 | 2 / 106 | 0.21 (0.01,4.32) |
| | Risedronate 2.5 mg/day versus Ibandronate 1 mg/month, IV | 1 | 40 / 309 | 35 / 317 | 1.17 (0.77,1.79) |
| | Risedronate 2.5 mg/day versus Ibandronate 0.5 mg/month, IV | 1 | 40 / 309 | 43 /324 | 0.98 (0.65,1.46) |
| | Risedronate 17.5 mg/week versus (RISW17.5 + Menatetrenone 45 mg/day) | 2 | 86 / 870 | 98 / 836 | 0.84 (0.64,1.11) |
| | Risedronate 2.5 mg/day versus Ibandronate 1 mg/month, IV | | - 3 / 29 | - 4 / 26 | |
| | Risedronate 2.5 mg/day versus Ibandronate 0.5 mg/month, IV | | - 83 / 841* | - 94 / 810* | |
| Gastrointestinal adverse events | Risedronate 35 mg/week versus Alendronate 70 mg/week | 2 | 134 / 617 | 153 / 622 | 0.88 (0.72, 1.08) |
| | | | - 73 / 395 | - 91 / 403 | |
| | | | - 61 / 222* | - 62 / 219* | |
| | Risedronate 2.5 mg/day versus Etidronate 200 mg/day | 1 | 27 / 118 | 23 / 117 | 1.16 (0.71, 1.91) |
| | Risedronate 17.5 mg/week versus (Risedronate 17.5 mg/week + Menatetrenone 45 mg/day) | 1 | 24 / 943† | 38 / 931† | 0.62 (0.38, 1.03) |
| Atypical femoral fracture | Risedronate 35 mg/week versus Alendronate 70 mg/week | 4 | 0 / 167 | 0 / 275 | NE |
| | | | - 0 / 52 | - 0 / 60 | |
| | | | - 0 / 25* | - 0 / 25* | |
| | | | - 0 / 32 | - 0 / 133 | |

(Continued)

| | | | | | |
|---|---|---|---|---|---|
| | | | - 0 / 58 | - 0 / 57 | |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 2 | 0 / 90 | 0 / 90 | NE |
| | | | - 0 / 32 | - 0 / 33 | |
| | | | - 0 / 58 | - 0 / 57 | |
| | Risedronate 150 mg/month versus Denosumab 60 mg/6m, sc | 1 | 0 / 429 | 0 / 429 | NE |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 1 | 0 / 680 | 0 / 680 | NE |
| | Risedronate 2.5 mg/day versus Ibandronate 1 mg/month, IV | 1 | 0 / 371 | 0 / 381 | NE |
| | Risedronate 2.5 mg/day versus Ibandronate 0.5 mg/month, IV | 1 | 0 / 371 | 0 /389 | NE |
| Acute phase reaction | Risedronate 35 mg/week versus Alendronate 70 mg/week | 1 | 1 / 58 | 2 / 57 | 0.49 (0.05, 5.27) |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 1 | 1 / 58 | 7 / 57 | 0.14 (0.02, 1.11) |
| Osteonecrosis of the jaw | Risedronate 150 mg/month versus Denosumab 60 mg/6m, sc | 1 | 0 / 429 | 0 / 429 | NE |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 1 | 0 / 680 | 0 / 680 | NE |
| | Risedronate 2.5 mg/day versus Ibandronate 1 mg/month, IV | 1 | 0 / 371 | 0 / 381 | NE |
| | Risedronate 2.5 mg/day versus Ibandronate 0.5 mg/month, IV | 1 | 0 / 371 | 0 / 389 | NE |
| Atrial fibrillation | Risedronate 35 mg/week versus Alendronate 70 mg/week | 1 | 1 / 58 | 2 / 57 | 0.49 (0.05, 5.27) |
| | Risedronate 35 mg/week versus Ibandronate 150 mg/month | 1 | 1 / 58 | 1 / 57 | 0.98 (0.06,15.34) |
| | Risedronate 150 mg/month versus Denosumab 60 mg/6 months, sc | 1 | 0 / 429 | 2 / 429 | 0.20 (0.01, 4.15) |
| | Risedronate 35 mg/week versus Teriparatide 20 µg/day, sc | 2 | 6 / 1033 | 5 / 1043 | 1.19 (0.39, 3.69) |
| | | | - 3 / 350 | - 0 / 360 | |
| | | | - 3 / 683 | - 5 / 683 | |

* In Hosking 2003 and Sarioglu 2006, rIsedonate 5 mg/day was compared with alendronate 70 mg/week.

† Risedronate 2.5 mg/day or 17.5 mg/week was used in two arms (Tanaka 2017).

IV= intravenous injection; sc: subcutaneous injection.

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 28 July 2022 | Amended | Authorship updated |

## HISTORY

Review first published: Issue 4, 2003

| Date | Event | Description |
|---|---|---|
| 24 March 2021 | New search has been performed | Literature search was updated. |
| 5 June 2019 | New citation required and conclusions have changed | Review updated to the latest Cochrane Musculoskeletal methods |
| 5 June 2019 | New citation required and conclusions have changed | Updated review with literature search and included studies not reporting outcome of interest |
| 6 August 2017 | New search has been performed | Updated review with literature search |
| 28 June 2012 | New search has been performed | Updated review with literature search with a broader scope, including head-to-head comparisons |
| 13 August 2008 | Amended | Absolute event rates included in the Plain language summary |
| 28 May 2008 | Amended | Converted to new review format. CMSG ID C072-R |
| 14 November 2007 | New citation required and conclusions have changed | See published notes for details on update. |

## CONTRIBUTIONS OF AUTHORS

George Wells was involved in the conception, design and implementation of the project and contributed significantly to the writing of the report.

Shu-Ching Hsieh was involved with the conception of the review, literature screening, data abstraction an analysis, risk of bias assessment, interpretation and writing of the final report.

Carine Zheng was involved with the conception of the review, literature screening and study selection, data abstraction, and risk of bias assessment.

Joan Peterson contributed to literature screening and study selection, data extraction, risk of bias assessment, and review of the final report.

Wenfei Liu contributed to data abstraction and risk of bias assessment.

Peter Tugwell provided clinical rheumatology expertise and methodological guidance, and review of the final report.

## DECLARATIONS OF INTEREST

None at present.

This current review was updated without the support of any industry sponsor.

## SOURCES OF SUPPORT

### Internal sources

- Ottawa Health Research Institute, Canada

  The views expressed in this report are those of the authors and not necessarily those of the Ottawa Health Research Institute.

### External sources

- Canadian Agency for Drugs and Technologies in Health, Canada

  This review was partly supported by the Canadian Agency for Drugs and Technologies in Health who has no responsibility for the views of this review.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to the changes made in accordance with the updated Cochrane review methodologies (Deeks 2019), there were six general differences in the manner two reviews were conducted.

1) We included articles published after the previous review was completed (updated to 05 Jun 2019).

2) We included all active-controlled trials of risedronate in addition to those that were placebo-controlled.

3) Following the MECIR standards (Higgins 2021), 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 BMD cut off value (2.5 versus 2 SD), an older age (75 versus 62) and the elimination of the 20% baseline fracture criteria (Figure 1).

5) We made the following changes to our outcome measures. For efficacy, we divided vertebral fractures into radiographic/morphometric and clinical, each with an explicit definition and added health-related quality of life. We moved radiographic fractures into minor outcomes. For safety outcomes, the current reviews added serious adverse events, gastrointestinal adverse events, acute phase reaction, osteonecrosis of the jaw, atypical femoral fractures and atrial fibrillation to 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.

6) We made a number of changes to our analyses. We included risedronate 2.5 mg/day in the base case instead of analysing it as a subgroup. We also added a 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 base case. The random-effects versus fixed-effect comparison was removed because the circumstances under which one or the other would be used were clearly described and, in the previous review, the results obtained from two models were similar. The test of using different baseline vertebral fracture to define a secondary prevention (i.e.100%, >80%, > 60%, > 40%, > 20%) was removed because a criterion based on a percentage of baseline vertebral fracture was not included in the hierarchical classification algorithm. Finally, 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 McClung 2001 study from the base case analysis.

## NOTES

This review updated a previously published review (Cranney 2003; Cranney 2006; Wells 2008) of risedronate conceived, conducted and completed, in part, by the authors of this report. Given the different review scope, our updated literature search retrieved an additional eight trials reporting data for pair-wise comparison of risedronate versus placebo, among which one was primary prevention trial (Välimäki 2007) and seven were secondary prevention trials (Bala 2014; Dobnig 2006; Dundar 2009; Hosking 2003; Leung 2005; Li 2005; Ohtori 2013). One study included in the previous review was found to report data covering one year of no treatment period so was excluded from analysis (Clemmesen 1997). All three primary prevention trials (Harris 2001; Muscoso 2004; Rosen 2005) and 18 secondary prevention trials contributing head-to-head comparisons of risedronate were newly retrieved for this update review (Akyol 2006; Anastasilakis 2008a; Atmaca 2006; Fukunaga 2002; Galesanu 2011; Hadji 2012; Hosking 2003; Kasukawa 2014; Kendler 2018; Nakamura 2013; NCT00365456; Ohtori 2013; Paggiosi 2014a; Reid 2006; Roux 2014; Sarioglu 2006; Tanaka 2017; Yanik 2008).

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Hip Fractures; *Osteoporosis; *Osteoporosis, Postmenopausal [complications] [drug therapy] [prevention & control]; *Osteoporotic Fractures [prevention & control]; Postmenopause; *Radius Fractures; Risedronic Acid [adverse effects]; Secondary Prevention; *Spinal Fractures [prevention & control]; *Wrist Injuries

### MeSH check words

Aged; Female; Humans