# Contents

# 1 Executive Summary

## 1.1 Aim of the report

To systematically review the clinical effectiveness of bisphosphonates for the treatment of osteoporosis in MA Servier Protelos.

## 1.2 Methods

A systematic review was undertaken to compare the effectiveness of bisphosphonates for the treatment of osteoporosis in MA Servier Protelos

### 1.2.1 Data sources

Major electronic databases were searched. Unpublished evidence such as conference abstracts, published reviews, and company submissions to the regulatory agencies (FDA review, EMEA - EPAR) were also reviewed.

### 1.2.2 Review methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and meta-analysis.

### 1.2.3 Trial selection

Trials were included if they fulfilled the following criteria:

1. **Types of intervention**: studies in which bisphosphonates was used.
2. **Types of participants**: only those studies were included in which the participants had been diagnosed as having established osteoporosis.
3. **Outcome measures**: all studies were included in which clinical events were reported.
4. **Study design**: only randomised controlled trials (RCTs) were included. Trials were accepted as RCTs if the allocation of patients to treatment groups was described as randomised.

### 1.2.4 Data synthesis

The clinical effectiveness of bisphosphonates was synthesised firstly through a narrative review with full tabulation of the results of the included studies and secondly by meta-analysis.

## 1.3 Results

In all 35 randomised controlled trials (RCTs) were included in this review of clinical effects of bisphosphonates. These included 29 studies of **biphosphonate**involving 25358 patients and 6 studies of **strontium ranelate**involving 7078 patients.
Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).

### 1.3.1 Biphosphonate

Reports of 29 trials (covering 31 comparisons and including 25358 patients) were identified . Among these comparisons, 8 trials are about alendronate , 3 about etidronate , one about ibandronate and 6 about risedronate.
After selection 8 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

#### Alendronate

Results obtained with alendronate for all the endpoints with data in at least one trial are summarized table **??**.

***Table 1.1:*** *Results summary - Alendronate*

| **Benefit** | **Harmful** | **No evidence** |
|---|---|---|
| | *Alendronate versus placebo* | |
| ↓ vertebral fractures<br>RR=0.54¶ [0.44;0.66] k=5<br>↓ clinical vertebral fractures<br>RR=0.45¶ [0.28;0.74] k=1<br>↓ hip fractures<br>RR=0.62* [0.41;0.96] k=5<br>↓ non vertebral fractures<br>RR=0.82† [0.72;0.94] k=6<br>↓ 1-year non vertebral fracture<br>RR=0.52* [0.30;0.89] k=1<br>↓ morphometric vertebral fractures<br>RR=0.53¶ [0.43;0.65] k=3 | | → 1-year vertebral fracture<br>RR=1.03NS [0.02;50.43] k=1 |

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

**H**: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

#### Etidronate

Results obtained with etidronate for all the endpoints with data in at least one trial are summarized table **??**.

***Table 1.2:*** *Results summary - Etidronate*

| **Benefit** | **Harmful** | **No evidence** |
|---|---|---|
| | *Etidronate versus control* | |
| | | → vertebral fractures<br>RR=0.15NS [0.01;2.95] k=1 |
| | *Etidronate versus placebo* | |
| | | → vertebral fractures<br>RR=0.64NS [0.18;2.26] k=1<br>→ hip fractures<br>RR=0.50NS [0.05;5.25] k=1<br>→ non vertebral fractures<br>RR=0.83NS [0.28;2.46] k=1 |

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

**H**: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

#### Ibandronate

Results obtained with ibandronate for all the endpoints with data in at least one trial are summarized table **??**.

***Table 1.3:*** *Results summary - Ibandronate*

| Benefit | Harmful | No evidence |
|---|---|---|
| | *Ibandronate versus placebo* | |
| ↓ morphometric vertebral fractures<br>RR=0.51¶ [0.34;0.74] k=1 | | → hip fractures<br>RR=0.67NS [0.19;2.35] k=1<br>→ major non vertebral fractures<br>RR=1.14NS [0.82;1.57] k=1<br>→ non vertebral fractures<br>RR=1.14NS [0.82;1.57] k=1<br>→ 1-year vertebral fracture<br>RR=0.62NS [0.28;1.37] k=1 |

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

**H**: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

### Risedronate

Results obtained with risedronate for all the endpoints with data in at least one trial are summarized table **??**.

***Table 1.4:*** *Results summary - Risedronate*

| Benefit | Harmful | No evidence |
|---|---|---|
| | *Risedronate versus placebo* | |
| ↓ vertebral fractures<br>RR=0.64¶ [0.53;0.77] k=4<br>↓ hip fractures<br>RR=0.68* [0.50;0.92] k=3<br>↓ major non vertebral fractures<br>RR=0.76¶ [0.65;0.89] k=3<br>↓ non vertebral fractures<br>RR=0.77¶ [0.66;0.89] k=6<br>↓ 1-year vertebral fracture<br>RR=0.40¶ [0.27;0.59] k=2<br>↓ morphometric vertebral fractures<br>RR=0.66† [0.49;0.90] k=1 | | |

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

**H**: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

## 1.3.2 Strontium ranelate

Reports of 6 trials (covering 6 comparisons and including 7078 patients) were identified .
Among these comparisons, 4 trials are about strontium ranelate.
After selection 2 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with strontium ranelate for all the endpoints with data in at least one trial are summarized table **??**.

***Table 1.5:*** *Results summary - Strontium ranelate*

| Benefit | Harmful | No evidence |
|---|---|---|
| | *Strontium ranelate versus placebo* | |

continued...

| Benefit | Harmful | No evidence |
|---|---|---|
| ↓ vertebral fractures<br>RR=0.60¶ [0.52;0.69] k=2 | | → hip fractures<br>RR=0.85NS [0.61;1.19] k=1 |
| ↓ clinical vertebral fractures<br>RR=0.62¶ [0.47;0.82] k=1 | | |
| ↓ major non vertebral fractures<br>RR=0.86* [0.73;1.00] k=2 | | |
| ↓ non vertebral fractures<br>RR=0.87* [0.76;1.00] k=2 | | |
| ↓ 1-year vertebral fracture<br>RR=0.53¶ [0.42;0.68] k=2 | | |
| ↓ morphometric vertebral fractures<br>RR=0.62¶ [0.54;0.71] k=3 | | |

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

**H**: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

# Part I

# Biphosphonate

# 2 Overview of biphosphonate

## 2.1 Included trials

A total of 18 randomized comparisons which enrolled 25358 patients were identified. In all, 8 randomized comparisons concerned alendronate , 3 etidronate , one ibandronate and 6 risedronate.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for alendronate, in section **??** (page **??**) for etidronate, in section **??** (page **??**) for ibandronate and in section **??** (page **??**) for risedronate.

The average study size was 1408 patients (range 35 to 9331). The first study was published in 1990, and the last study was published in 2005.
A total of 16 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

## 2.2 Summary of meta-analysis results

The meta-analysis of the available trials about biphosphonate provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

### 2.2.1 Alendronate

**Alendronate** was superior to **placebo** in terms of vertebral fractures (RR=0.54, 95% CI 0.44 to 0.66, p=0.0000, 5 trials), clinical vertebral fractures (RR=0.45, 95% CI 0.28 to 0.74, p=0.0000, 1 trial), hip fractures (RR=0.62, 95% CI 0.41 to 0.96, p=0.0335, 5 trials), non vertebral fractures (RR=0.82, 95% CI 0.72 to 0.94, p=0.0033, 6 trials), 1-year non vertebral fracture (RR=0.52, 95% CI 0.30 to 0.89, p=0.0181, 1 trial)and morphometric vertebral fractures (RR=0.53, 95% CI 0.43 to 0.65, p=0.0000, 3 trials). However, no significant difference was found on 1-year vertebral fracture (RR=1.03, 95% CI 0.02 to 50.43, p=0.9868, 1 trial).

### 2.2.2 Etidronate

No significant difference was found between **etidronate** and **control** in terms of vertebral fractures (RR=0.15, 95% CI 0.01 to 2.95, p=0.2137, 1 trial).

No significant difference was found between **etidronate** and **placebo** in terms of vertebral fractures (RR=0.64, 95% CI 0.18 to 2.26, p=0.4834, 1 trial), hip fractures (RR=0.50, 95% CI 0.05 to 5.25, p=0.5634, 1 trial)and non vertebral fractures (RR=0.83, 95% CI 0.28 to 2.46, p=0.7417, 1 trial).

### 2.2.3 Ibandronate

**Ibandronate** was superior to **placebo** in terms of morphometric vertebral fractures (RR=0.51, 95% CI 0.34 to 0.74, p=0.0000, 1 trial). However, no significant difference was found on hip fractures (RR=0.67, 95% CI 0.19 to 2.35, p=0.5268, 1 trial), major non vertebral fractures (RR=1.14, 95% CI 0.82 to 1.57, p=0.4360, 1 trial), non vertebral fractures (RR=1.14, 95% CI

0.82 to 1.57, p=0.4360, 1 trial)and 1-year vertebral fracture (RR=0.62, 95% CI 0.28 to 1.37, p=0.2386, 1 trial).

### 2.2.4 Risedronate

**Risedronate** was superior to **placebo** in terms of vertebral fractures (RR=0.64, 95% CI 0.53 to 0.77, p=0.0000, 4 trials), hip fractures (RR=0.68, 95% CI 0.50 to 0.92, p=0.0120, 3 trials), major non vertebral fractures (RR=0.76, 95% CI 0.65 to 0.89, p=0.0000, 3 trials), non vertebral fractures (RR=0.77, 95% CI 0.66 to 0.89, p=0.0000, 6 trials), 1-year vertebral fracture (RR=0.40, 95% CI 0.27 to 0.59, p=0.0000, 2 trials)and morphometric vertebral fractures (RR=0.66, 95% CI 0.49 to 0.90, p=0.0086, 1 trial).

***Table 2.1:*** *Main study characteristics - biphosphonate*

| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| **Alendronate** | | | |
| ***Alendronate versus placebo*** | | | |
| * alendronate phase 3 (Liberman), 1995 [**?**]<br>n = 597 vs. 397 | women with postmenopausal osteoporosis | alendronate (5 or 10 mg daily for three years, or 20 mg for two years followed by 5 mg for one year<br>**versus**<br>placebo<br>treatment duration: 3 years | double-blind<br>parallel groups<br>Primary endpoint: bone mineral density of the spine<br>multicenter,USA, Australia, Canada, Europe, Israel, Mexico, NZ, SA<br>included in Jansen meta-analysis: yes |
| * FIT 2 (Cummings), 1998 [**?**]<br>n = 2214 vs. 2218 | women aged 54 to 81 years with a femoral neck BMD of 0.68 g/cm2 or less (Hologic) but no vertebral fracture | 5 mg/d of alendronate sodium for 2 years followed by 10 mg/d for the remainder of the trial<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: clinical fracture<br>11 centres,USA<br>included in Jansen meta-analysis: yes |
| * FIT1 (Black), 1996 [**?**]<br>n = 1022 vs. 1005 | women aged 55-81 with low femoral-neck BMD with at least one vertebral fracture | alendronate (initially 5 mg daily) was increased (to 10 mg daily) at 24 months<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: new vertebral fracture<br>multicentre,USA<br>fracture definition: defined by<br>included in Jansen meta-analysis: yes |
| Adami, 1995 [**?**]<br>n = 140 vs. 71 | postmenopausal women between the ages of 48 and 76 with spinal bone mineral density >or = 2 SD below adult mean peak in the two-year | alendronate 10 or 20 mg/day<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: lumbar spine BMD<br>9 centres,Italy |
| Bone, 1997 [**?**]<br>n = 268 vs. 91 | women with lumbar spine BMD at least 2.0 SD below the peak young adult mean | 1.0, 2.5, or 5.0 mg alendronate daily<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: NA<br>15 centres,USA |

continued...

| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| Chesnut 10mg, 1995 [?]<br>n = 30 vs. 31 | postmenopausal women, aged 42 to 75 years, with low bone mineral density of the lumbar spine | alendronate 10 mg daily for 2 years<br>**versus**<br>placebo<br>treatment duration: 2 years | double-blind<br>parallel groups<br>Primary endpoint: BMD<br>7 centres,USA |
| FOSIT (Pols), 1999 [?]<br>n = 950 vs. 958 | postmenopausal women with lumbar spine BMD 2 standard deviations or more below the premenopausal adult mean | oral alendronate 10 mg for 12 months<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: BMD<br>153 centres,34 countries |
| Greenspan, 1998 [?]<br>n = 60 vs. 60 | community-dwelling, ambulatory women 65 years of age and older | alendronate for 2.5 years<br>**versus**<br>placebo<br>treatment duration: 2.5 years | double-blind<br>parallel groups<br>Primary endpoint: NA<br>single center,USA |
| **Etidronate** | | | |
| ***Etidronate versus control*** | | | |
| Montessori, 1997 [?]<br>n = 40 vs. 40 | osteoporotic postmenopausal women with or without fractures | intermittent, cyclic etidronate<br>**versus**<br>calcium alone | open<br>cross over<br>Primary endpoint: not defined<br>2 centres,The Netherlands |
| ***Etidronate versus placebo*** | | | |
| Storm, 1990 [?]<br>n = 33 vs. 33 | women with postmenopausal osteoporosis | intermittent cyclical etidronate 400mg daily for 2 weeks followed by a 13-week period with no drugs, for 150 weeks<br>**versus**<br>placebo | double-blind<br>parallel groups<br>single center,Denmark |
| Wimalawansa, 1998 [?]<br>n = 17 vs. 18 | postmenopausal women with established osteoporosis | combined HRT plus etidronate intermittent cyclical etidronate for 4 years<br>**versus**<br>control | open<br>parallel groups<br>Primary endpoint: NA |
| **Ibandronate** | | | |

continued...

| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| ***Ibandronate versus placebo*** | | | |
| * BONE (Chesnut) daily ibandronate, 2005 [**?**]<br>n = 982 vs. 982 | postmenopausal women (age 55 years-80 years; >or = 5 years since menopause) with osteoporosis (low lumbar spine bone mineral density and one to four prevalent vertebral fractures [T4-L4]). | oral daily ibandronate (2.5 mg)<br>**versus**<br>placebo<br>treatment duration: 3 years | double-blind<br>parallel groups<br>Primary endpoint: morphometric vertebral fractures<br>73 centres,USA, Canada, Europe<br>included in Jansen meta-analysis: yes |
| **Risedronate** | | | |
| ***Risedronate versus placebo*** | | | |
| * VERT (Harris) 5 mg, 1999 [**?**]<br>n = 813 vs. 820 | ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline | oral treatment for 3 years with risedronate 5 mg/d<br>**versus**<br>placebo<br>treatment duration: 3 years | double-blind<br>parallel groups<br>Primary endpoint: vertebral fracture<br>110 centres,North America<br>included in Jansen meta-analysis: yes |
| * VERT europe (Reginster) 5mg, 2000 [**?**]<br>n = 407 vs. 407 | postmenopausal women with two or more prevalent vertebral fractures | risedronate 5 mg/day for 3 years<br>**versus**<br>placebo<br>treatment duration: 3 y | double-blind<br>parallel groups<br>Primary endpoint: vertebral fracture<br>80 centres,Europe, Australia<br>included in Jansen meta-analysis: yes |
| BMD-MN (Fogelman), 2000 [**?**]<br>n = 363 vs. 180 | postmenopausal women with low bone mass | risedronate 2.5 mg/d or risedronate 5 mg/d<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: bone mineral density<br>13 centres,France, UK, the Netherlands, Belgium, Germany |
| Clemmesen, 1997 [**?**]<br>n = 88 vs. 44 | patients with postmenopausal osteoporosis and at least one, but no more than four prevalent vertebral fractures at baseline | 2.5 mg continuous risedronate or 2.5 mg cyclic risedronate for 2 years<br>**versus**<br>placebo<br>treatment duration: 2 years | double-blind<br>parallel groups<br>Primary endpoint: none defined<br>2 centres,Denmark, Belgium |

continued...

| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| McClung (overall), 2001 [**?**]<br>n = 6197 vs. 3134 | women 70 to 79 years old with osteoporosis and women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck | oral risedronate (2.5 or 5.0 mg daily)<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: hip fracture<br>183 centres,Noth America, Europe, New Zealand, Australia |
| risedronate dose ranging (McClung), 1999 [**?**]<br>n = 428 vs. 220 | menopausal women with low BMD (T-score <-2) | risedronate 2.5 mg/d or risedronate 5 mg/d for up to 18 months<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: BMD<br>multicentre, |

***Table 2.2:*** *Summary of all results for alendronate*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***alendronate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.54 | 0.44;0.66 | 0.0000 | 0.9861 (0.00) | 5 | 7475 |
| clinical vertebral fractures | RR=0.45 | 0.28;0.74 | 0.0000 | 1.0000 (0.00) | 1 | 2027 |
| hip fractures | RR=0.62 | 0.41;0.96 | 0.0335 | 0.7601 (0.00) | 5 | 9481 |
| non vertebral fractures | RR=0.82 | 0.72;0.94 | 0.0033 | 0.3728 (0.07) | 6 | 9840 |
| 1-year vertebral fracture | RR=1.03 | 0.02;50.43 | 0.9868 | 1.0000 (0.00) | 1 | 61 |
| 1-year non vertebral fracture | RR=0.52 | 0.30;0.89 | 0.0181 | 1.0000 (0.00) | 1 | 1908 |
| morphometric vertebral fractures | RR=0.53 | 0.43;0.65 | 0.0000 | 0.9980 (0.00) | 3 | 7042 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

***Table 2.3:*** *Summary of all results for etidronate*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***etidronate versus control*** | | | | | | |
| vertebral fractures | RR=0.15 | 0.01;2.95 | 0.2137 | 1.0000 (0.00) | 1 | 71 |
| ***etidronate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.64 | 0.18;2.26 | 0.4834 | 1.0000 (0.00) | 1 | 35 |
| hip fractures | RR=0.50 | 0.05;5.25 | 0.5634 | 1.0000 (0.00) | 1 | 66 |
| non vertebral fractures | RR=0.83 | 0.28;2.46 | 0.7417 | 1.0000 (0.00) | 1 | 66 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

***Table 2.4:*** *Summary of all results for ibandronate*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***ibandronate versus placebo*** | | | | | | |
| hip fractures | RR=0.67 | 0.19;2.35 | 0.5268 | 1.0000 (0.00) | 1 | 1952 |
| major non vertebral fractures | RR=1.14 | 0.82;1.57 | 0.4360 | 1.0000 (0.00) | 1 | 1952 |
| non vertebral fractures | RR=1.14 | 0.82;1.57 | 0.4360 | 1.0000 (0.00) | 1 | 1952 |
| 1-year vertebral fracture | RR=0.62 | 0.28;1.37 | 0.2386 | 1.0000 (0.00) | 1 | 1952 |
| morphometric vertebral fractures | RR=0.51 | 0.34;0.74 | 0.0000 | 1.0000 (0.00) | 1 | 1952 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

***Table 2.5:*** *Summary of all results for risedronate*

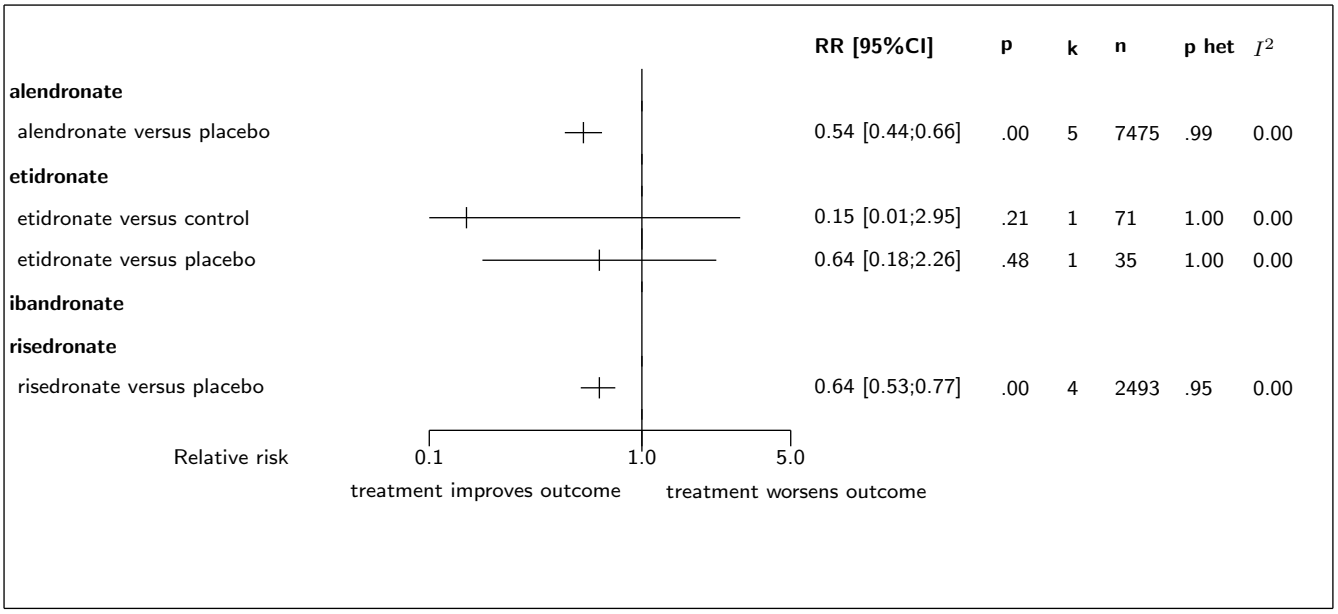
| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***risedronate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.64 | 0.53;0.77 | 0.0000 | 0.9452 (0.00) | 4 | 2493 |
| hip fractures | RR=0.68 | 0.50;0.92 | 0.0120 | 0.3136 (0.14) | 3 | 12601 |
| major non vertebral fractures | RR=0.76 | 0.65;0.89 | 0.0000 | 0.5765 (0.00) | 3 | 11770 |
| non vertebral fractures | RR=0.77 | 0.66;0.89 | 0.0000 | 0.6398 (0.00) | 6 | 12847 |
| 1-year vertebral fracture | RR=0.40 | 0.27;0.59 | 0.0000 | 0.7595 (0.00) | 2 | 1996 |
| morphometric vertebral fractures | RR=0.66 | 0.49;0.90 | 0.0086 | 1.0000 (0.00) | 1 | 1633 |

continued...

| Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|

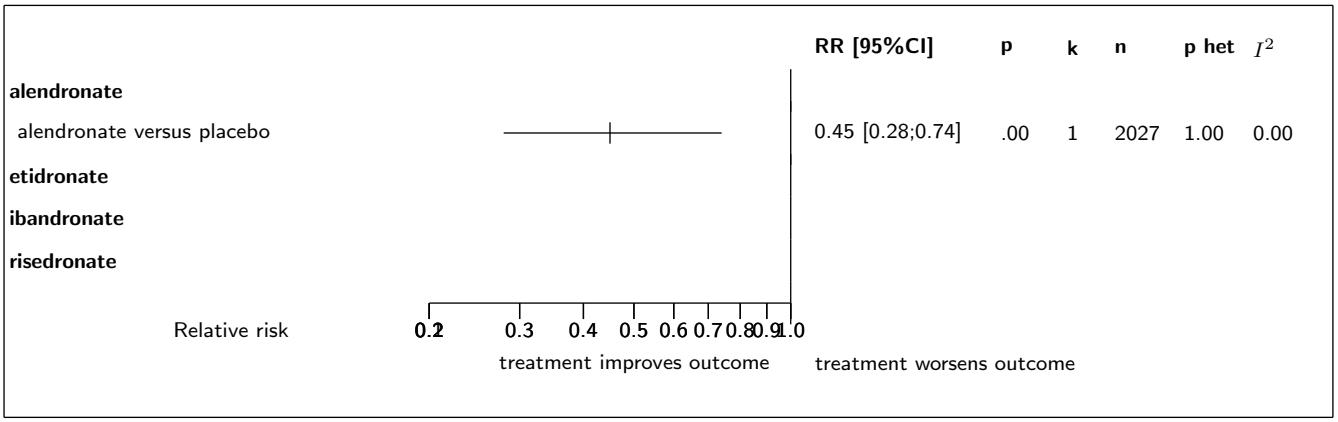
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

***Figure 2.1:*** *Forest's plot for vertebral fractures*



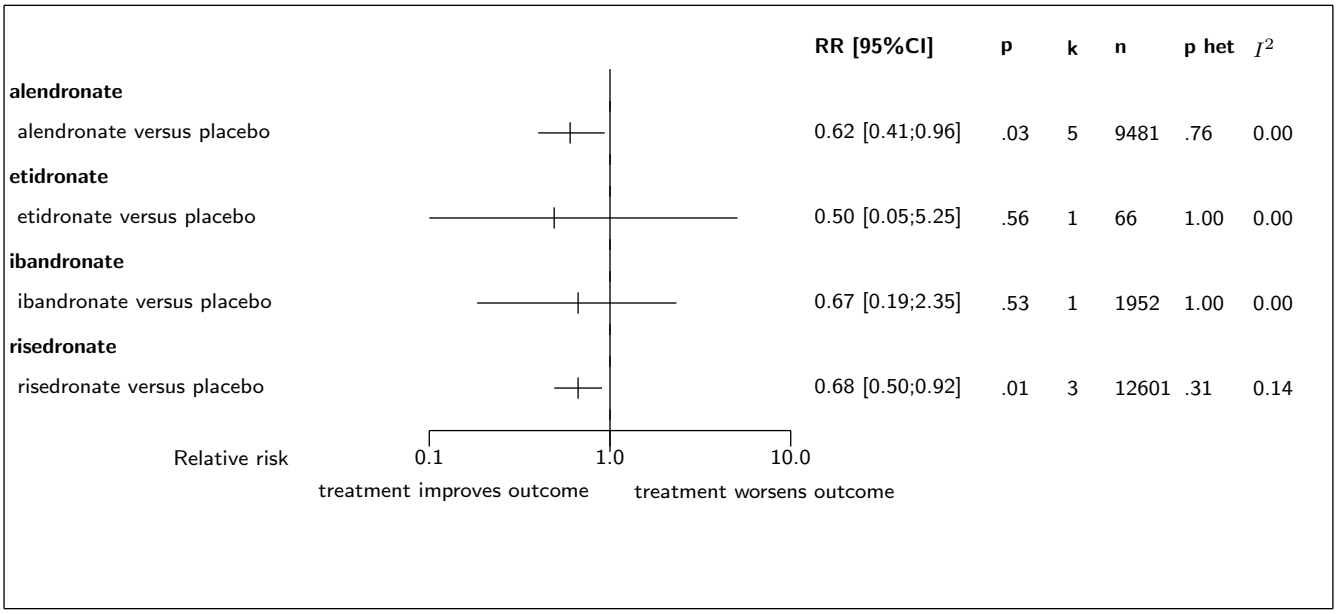

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.2:*** *Forest's plot for clinical vertebral fractures*



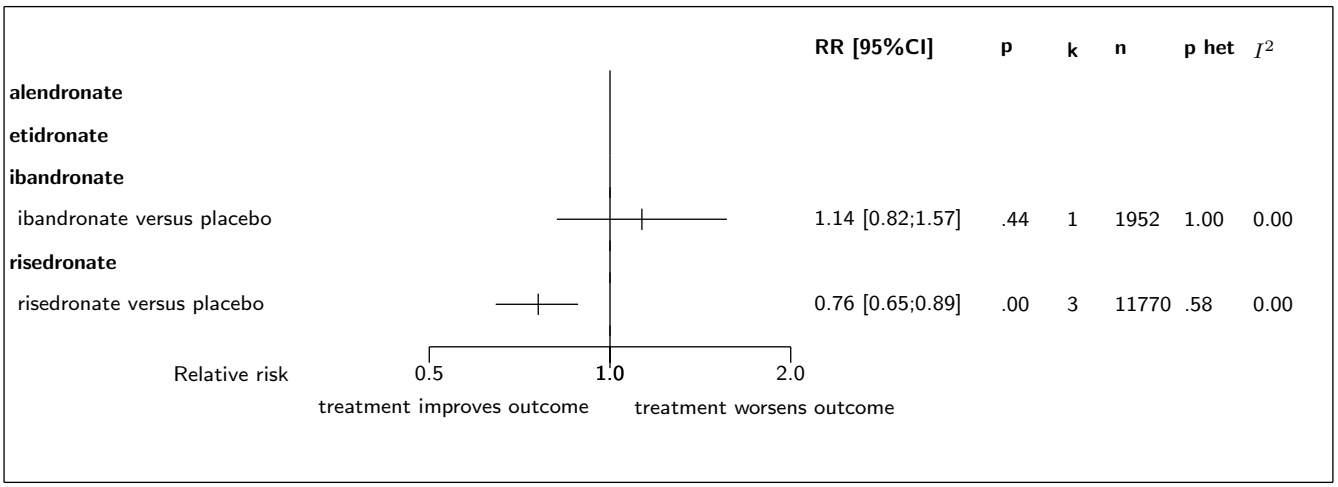

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.3:*** *Forest's plot for hip fractures*



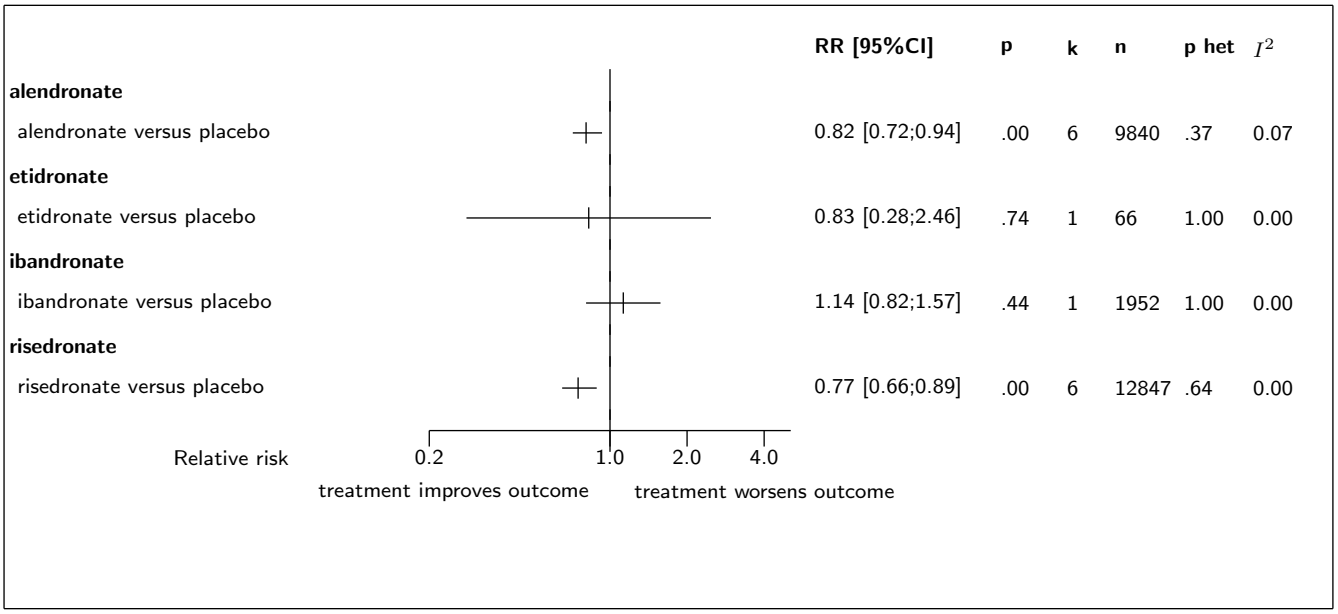

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.4:*** *Forest's plot for major non vertebral fractures*



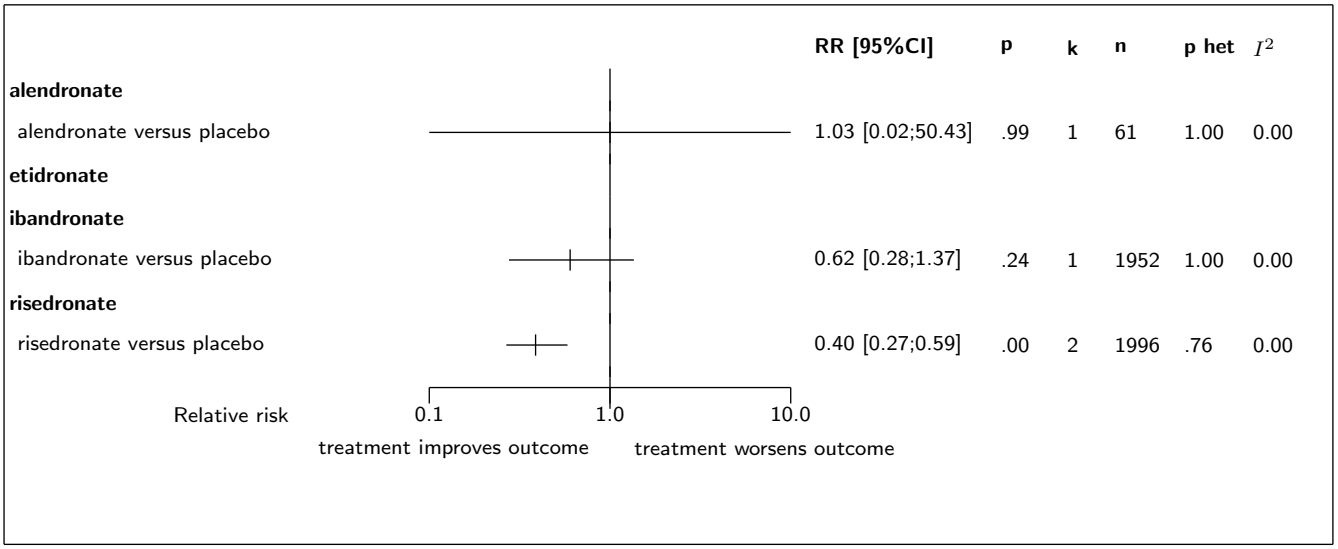

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.5:*** *Forest's plot for non vertebral fractures*



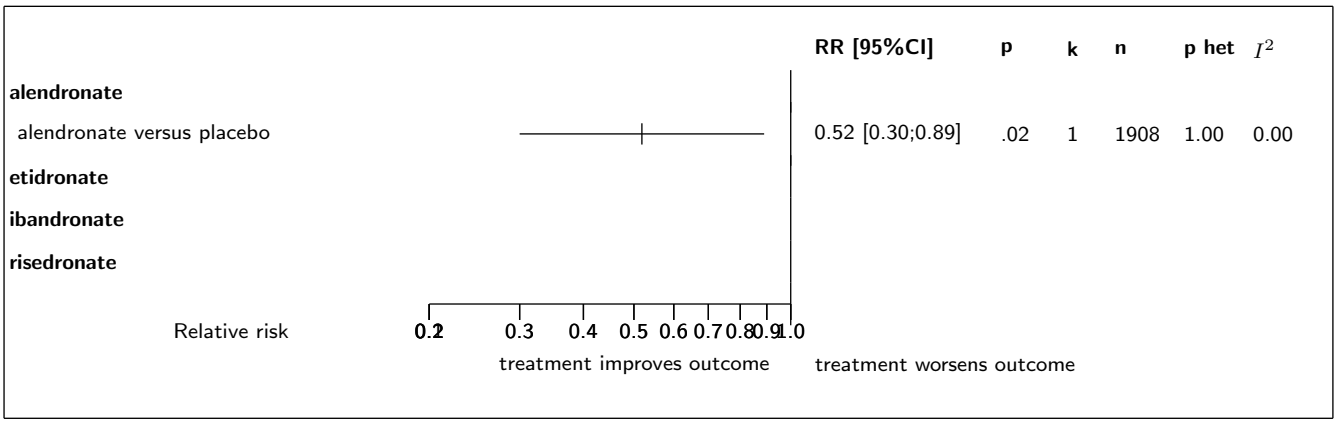

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.6:*** *Forest's plot for 1-year vertebral fracture*



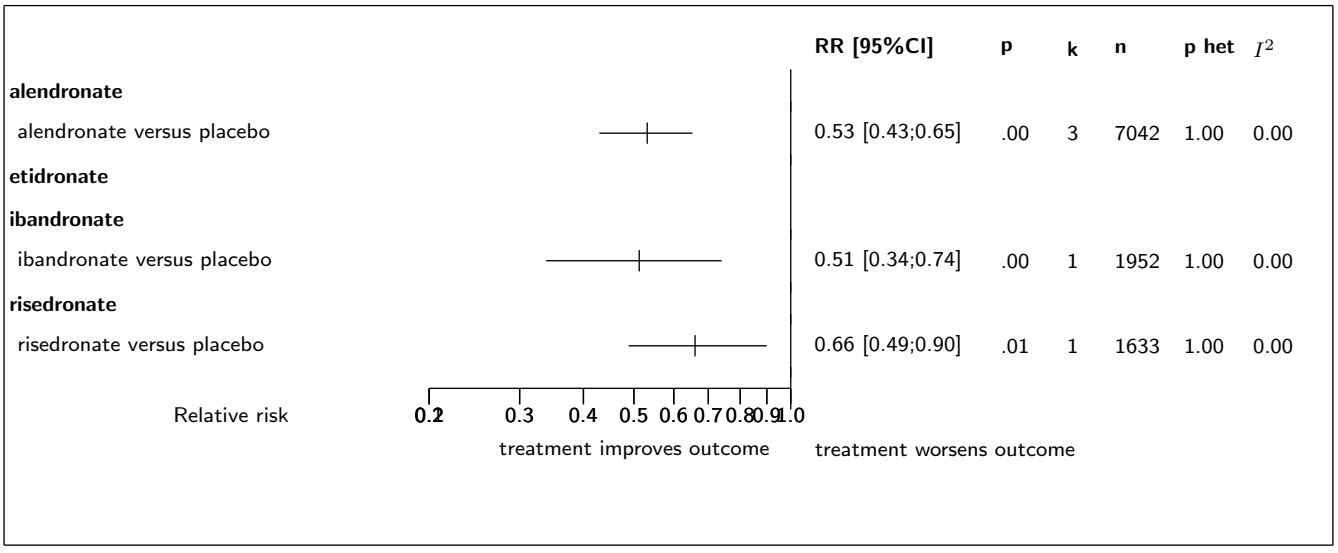

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.7:*** *Forest's plot for 1-year non vertebral fracture*




Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 2.8:*** *Forest's plot for morphometric vertebral fractures*




Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

# 3 Detailed results for alendronate

## 3.1 Available trials

A total of 8 RCTs which randomized 10112 patients were identified: all compared alendronate with placebo.
The average study size was 1264 patients (range 61 to 4432). The first study was published in 1995, and the last study was published in 1999.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Non vertebral fractures data was reported in 8 trials; 7 trials reported data on hip fractures; 7 trials reported data on vertebral fractures; 3 trials reported data on 1-year vertebral fracture; 3 trials reported data on morphometric vertebral fractures; 2 trials reported data on 1-year non vertebral fracture; and 1 trials reported data on clinical vertebral fractures.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of alendronate.

***Table 3.1:*** *Treatment description - biphosphonate - alendronate*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Alendronate versus placebo** | | |
| * alendronate phase 3 (Liberman) (1995) [**?**] | alendronate (5 or 10 mg daily for three years, or 20 mg for two years followed by 5 mg for one year<br>**Concomittant treatment:** 500mg of calcium daily | placebo |
| * FIT 2 (Cummings) (1998) [**?**] | 5 mg/d of alendronate sodium for 2 years followed by 10 mg/d for the remainder of the trial | placebo |
| * FIT1 (Black) (1996) [**?**] | alendronate (initially 5 mg daily) was increased (to 10 mg daily) at 24 months | placebo |
| Adami (1995) [**?**] [d] | alendronate 10 or 20 mg/day<br>**Concomittant treatment:** calcium 500mg daily | placebo |
| Bone (1997) [**?**] | 1.0, 2.5, or 5.0 mg alendronate daily<br>**Concomittant treatment:** calcium supplementcontaining 500 mg elemental calcium | placebo |
| Chesnut 10mg (1995) [**?**] [f] | alendronate 10 mg daily for 2 years<br>**Concomittant treatment:** 500mg of elemental calcium | placebo |
| FOSIT (Pols) (1999) [**?**] | oral alendronate 10 mg for 12 months<br>**Concomittant treatment:** elemental calcium 500mg daily | placebo |
| Greenspan (1998) [**?**] | alendronate for 2.5 years<br>5 mg daily increased to 101mg daily in November 1993, when data became available thatthe 10 mg dose of alendronate produced greater increasesin bone density than the 5 mg dose | placebo |

continued...

| Trial | Studied treatment | Control treatment |
|---|---|---|
| | **Concomittant treatment:** suplemental 250 mg of elemental calcium and 125 IU ofvitamin D to provide a total daily calcium intake of at least1000 mg | |

d) 4 arms: alendronate 10 mg/day, alendronate 20 mg/day, or open-label intranasal salmon calcitonin 100 IU/day; placebo f) 6 arms: placebo or 5 or 10 mg of alendronate, for 24 months; a fourth group received 40 mg of alendronate for 3 fourth group received 40 mg of alendronate for 3 months, followed by 2.5 mg for 21 months. The last 2 groups received 20 or 40 mg of alendronate for 12 months followed by placebo for 12 months.

***Table 3.2:*** *Descriptions of participants - biphosphonate - alendronate*

| Trial | Patients | |
|---|---|---|
| **Alendronate versus placebo** | | |
| * alendronate phase 3 (Liberman) (1995) [**?**] | Women with postmenopausal osteoporosis | |
| | **Inclusion criteria:** 45 to 80 years old; postmenopausal ( >=5 years since menopause); osteoporosis (defined as a bone mineral density of the lumbar spine that was at least 2.5 SD below the mean value in premenopausal white women) | **Exclusion criteria:** other causes of osteoporosis (e.g., treatment with glucocorticoids) or other disorders of bone and mineral metabolism (e.g., vitamin D deficiency, Pagets disease, or hyperparathyroidism); active peptic ulcer disease; abnormal renal function; abnormal hepatic function; abnormalities of the lumbar spine precluding the assessment of bone mineral density at a minimum of three lumbar vertebrae or a history of hip fracture; any prior treatment with bisphosphonates or treatment within the preceding 12 months with estrogen, progestin, calcitonin, fluoride, or an anabolic steroid. |
| * FIT 2 (Cummings) (1998) [**?**] | Women aged 54 to 81 years with a femoral neck BMD of 0.68 g/cm2 or less (Hologic) but no vertebral fracture | |
| | **Inclusion criteria:** | **Exclusion criteria:** recent peptic ulcers or ulcers that required hospitalization, dyspepsia requiring daily treatment, significant renal or hepatic dysfunction, medical problems that precluded 3 years of participation, severe malabsorption, blood pressure exceeding 210 mm Hg systolic or 105 mm Hg diastolic, myocardial infarction within 6 months, unstable angina, hypothyroidism, hyperthyroidism, or hyperparathyroidism; estrogen or calcitonin within the preceding 6 months or bisphosphonates or sodium fluoride ( >1 mg/d) at any time |
| * FIT1 (Black) (1996) [**?**] | Women aged 55-81 with low femoral-neck BMD with at least one vertebral fracture | |
| | **Inclusion criteria:** women aged between 55 and 81 years; postmenopausal for at least 2 years; femoral neck BMD of 068 g/cm2 or less (QDR-2000 Hologic, Waltham, MA, USA), about 21 SDs below peak bone mass based on the manufacturers normative data; at least one vertebral fracture at baseline | **Exclusion criteria:** peptic-ulcer disease (a single hospital admission for uppergastrointestinal bleeding or two or more documented ulcers within the preceding 5 years), dyspepsia requiring daily treatment, abnormal renal function (serum creatinine >144 mol/L), major medical problems that would be likely to preclude participation for 3 years, severe malabsorption syndrome, uncontrolled hypertension (blood pressure >210 mm Hg systolic or >105 mm Hg diastolic), myocardial infarction during the previous 6 months, unstable angina, or evidence of disturbed thyroid or parathyroid function; oestrogen or calcitonin within the preceding 6 months or bisphosphonates or sodium fluoride ( >1 mg daily for 2 weeks or longer) at any time |

continued...

| Trial | Patients | |
|---|---|---|
| Adami (1995) [?] | Postmenopausal women between the ages of 48 and 76 with spinal bone mineral density >or = 2 SD below adult mean peak in the two-year | |
| | **Inclusion criteria:** women between the ages of 48 and 76 years; at least 2 years past natural menopause; lumbar spine bone mineraldensity (BMD) >2 SD below the mean for youngpremenopausal women | **Exclusion criteria:** any secondary cause of osteoporosis, other metabolic bone disease, hyper- or hypothyrodism or any associated health problems taht could affect tehir participation in teh study |
| Bone (1997) [?] | Women with lumbar spine BMD at least 2.0 SD below the peak young adult mean | |
| | **Inclusion criteria:** good health apart from osteoporosis; lumbar spine BMD of 0.824 g/cm2 or less byHologic DXA or 0.944 g/cm2 or less by Lunar DXA (2.0 sd below mean peak levels); | **Exclusion criteria:** more than 1 lumbar crush fracture; spinal anatomy was otherwise unsuitable for DXA analysis; history of recent major gastrointestinal disease, such as peptic ulcer, esophageal disorder, or malabsorption, or had recently used a drug to inhibit gastric acid secretion for more than 2 weeks; chronic nonsteroidal antiinflammatory therapy or agents known to affect bone metabolism (such as etidronate, estrogen, glucocorticoids, fluoride, or calcitonin) |
| Chesnut 10mg (1995) [?] | Postmenopausal women, aged 42 to 75 years, with low bone mineral density of the lumbar spine | |
| | **Inclusion criteria:** healthy women aged 42 to 75 years; postmenopausal, with lumbar spine BMD <=0.88 g/cm2 (approximately 2 standard deviations below young, normal US white female mean BMD values) | **Exclusion criteria:** spine or hip fractures attribuable to osteoporosis |
| FOSIT (Pols) (1999) [?] | Postmenopausal women with lumbar spine BMD 2 standard deviations or more below the premenopausal adult mean | |
| | **Inclusion criteria:** postmenopausal for at least 3 years; not older than 85 years; BMD of the lumbar spine (L24) at least 2 standard deviations (SD) below the mean for mature, premenopausal women; good health and between 20% below and 50% above ideal body weight as defined in the Metropolitan Life Insurance Company Height and Weight Table | **Exclusion criteria:** metabolic bone disease other than postmenopausal osteoporosis; disturbed parathyroid or thyroid function; major gastrointestinal disease within the year before enrollment or use of a drug to inhibit gastric acid secretion for >2 weeks within 3 months of study entry; myocardial infarction within the year prior to enrollment; uncontrolled hypertension or untreated angina; significantly impaired renal function (serum creatinine >150 mmol/l); evidence of significant end organ disease |
| Greenspan (1998) [?] | Community-dwelling, ambulatory women 65 years of age and older | |
| | **Inclusion criteria:** no BMD criteria | **Exclusion criteria:** history of any illness affecting bone and mineral metabolism (e.g., renal failure, hepatic failure, active malignancy, current hyperthyroidism or hyperparathyroidism, or malabsorption); medications known to affect bone metabolism (e.g., glucocorticoids, anticonvulsants); treatement for osteoporosis with bisphosphonates, hormone replacement therapy, or calcitonin within 1 year of screening |

***Table 3.3:*** *Main patients characteristics - biphosphonate - alendronate*

| Trial | Characteristics |
|---|---|
| **Alendronate versus placebo** | |
| * alendronate phase 3 (Liberman), 1995 [?] | age (yr): 64 y<br>prevalent fractures (%): 21%<br>time since menopause (yr): 17 y<br>BMD: .82 g/cm2 (Lunar, lumbar spine)<br>low BMD as inclusion criteria: <-2.5 SD<br>low BMD as criteria: yes<br>prevalent fracture as criteria: no<br>inclusion without BMD: no |
| * FIT 2 (Cummings), 1998 [?] | age (yr): 67.7 y<br>prevalent fractures (%): 0%<br>BMD: .842 (Posterior-anterior spine)<br>low BMD as inclusion criteria: <0.68 g/cm2 (femoral neck, Hologic)<br>low BMD as criteria: yes<br>prevalent fracture as criteria: no<br>inclusion without BMD: no<br>prevalente fracture at baseline: 0% |
| * FIT1 (Black), 1996 [?] | age (yr): 71 y<br>prevalent fractures (%): 100%<br>BMD: .56 (femoral neck)<br>low BMD as inclusion criteria: yes<br>low BMD as criteria: yes<br>prevalent fracture as criteria: yes<br>prevalente fracture at baseline: 100% |
| Adami, 1995 [?] | age (yr): 59 y<br>prevalent fractures (%): 5%<br>time since menopause (yr): 11 y<br>BMD: .82 g/cm2 (Lunar, spine)<br>low BMD as inclusion criteria: <-2 SD (lumbar spine)<br>low BMD as criteria: yes<br>prevalent fracture as criteria: no<br>inclusion without BMD: no<br>prevalente fracture at baseline: 5% |
| Bone, 1997 [?] | age (yr): 71.1 yr<br>prevalent fractures (%): 35%<br>BMD: .71 g/cm2 (Hologic)<br>low BMD as inclusion criteria: <-2 SD ( <0.824 by Hologic, <0.944 by Lunar)<br>prevalente fracture at baseline: 35% |
| Chesnut 10mg, 1995 [?] | age (yr): 63.6 yr<br>time since menopause (yr): 16.9 yr<br>BMD: .750 g/cm2 (lumbar spine)<br>low BMD as inclusion criteria: <0.88 g/cm2 ( <2 SD)<br>low BMD as criteria: yes<br>prevalent fracture as criteria: no<br>inclusion without BMD: no<br>prevalente fracture at baseline: 0% |
| FOSIT (Pols), 1999 [?] | age (yr): 62.8 y<br>time since menopause (yr): 15.8 y<br>BMD: .83 (Lunar DPX)<br>low BMD as inclusion criteria: yes<br>low BMD as criteria: yes<br>prevalent fracture as criteria: no<br>inclusion without BMD: no<br>prevalente fracture at baseline: not specified |
| Greenspan, 1998 [?] | age (yr): 70 y<br>prevalent fractures (%): NA<br>time since menopause (yr): NA<br>BMD: 0.865 g/cm2 (PA spine, Hologic)<br>low BMD as inclusion criteria: no<br>low BMD as criteria: no<br>inclusion without BMD: yes |

***Table 3.4:*** *Design and methodological quality of trials - biphosphonate - alendronate*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Alendronate versus placebo** | | | | |
| * alendronate phase 3 (Liberman), 1995 [?] [(a)] n=994 | Parallel groups double-blind exploratory trial | 3 years | USA, Australia, Canada, Europe, Israel, Mexico, NZ, SA multicenter | Bone mineral density of the spine |
| * FIT 2 (Cummings), 1998 [?] n=4432 | Parallel groups double-blind confirmatory trial at low risk of bias | 4 years inclusion period: NA | USA 11 centres | clinical fracture |
| * FIT1 (Black), 1996 [?] n=2027 | Parallel groups double-blind confirmatory trial at low risk of bias | 3 years | USA multicentre | New vertebral fracture |
| Adami, 1995 [?] n=211 | Parallel groups double-blind exploratory trial | 2 years | Italy 9 centres | lumbar spine BMD |
| Bone, 1997 [?] n=359 | Parallel groups double-blind exploratory trial | 2 years | USA 15 centres | NA |
| Chesnut 10mg, 1995 [?] n=61 | Parallel groups double-blind exploratory trial | 2 years | USA 7 centres | BMD |
| FOSIT (Pols), 1999 [?] n=1908 | Parallel groups double-blind exploratory trial | 1 year | 34 countries 153 centres | BMD |
| Greenspan, 1998 [?] n=120 | Parallel groups double-blind exploratory trial | 2.5 years | USA single center | NA |

a) dose ranging

## 3.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Alendronate versus placebo

A total of 5 of the 8 studies eligible for this comparison provided data on **vertebral fractures**. The analysis detected a statistically significant difference in favor of alendronate in vertebral fractures, with a RR of 0.54 (95% CI 0.44 to 0.66, p=0.0000). No heterogeneity was detected (p = 0.9861, $I^2$ = 0.00%).

Only one of the 8 studies eligible for this comparison provided data on **clinical vertebral fractures**. The analysis detected a statistically significant difference in favor of alendronate in clinical vertebral fractures, with a RR of 0.45 (95% CI 0.28 to 0.74, p=0.0000).

A total of 5 of the 8 studies eligible for this comparison provided data on **hip fractures**. The analysis detected a statistically significant difference in favor of alendronate in hip fractures, with a RR of 0.62 (95% CI 0.41 to 0.96, p=0.0335). No heterogeneity was detected (p = 0.7601,

$I^2 = 0.00\%$).
A total of 6 of the 8 studies eligible for this comparison provided data on **non vertebral fractures**. The analysis detected a statistically significant difference in favor of alendronate in non vertebral fractures, with a RR of 0.82 (95% CI 0.72 to 0.94, p=0.0033). No heterogeneity was detected (p = 0.3728, $I^2 = 0.07\%$).
Only one of the 8 studies eligible for this comparison provided data on **1-year vertebral fracture**. No statistically significant difference between the groups was found in 1-year vertebral fracture, with a RR of 1.03 (95% CI 0.02 to 50.43, p=0.9868).
Only one of the 8 studies eligible for this comparison provided data on **1-year non vertebral fracture**. The analysis detected a statistically significant difference in favor of alendronate in 1-year non vertebral fracture, with a RR of 0.52 (95% CI 0.30 to 0.89, p=0.0181).
A total of 3 of the 8 studies eligible for this comparison provided data on **morphometric vertebral fractures**. The analysis detected a statistically significant difference in favor of alendronate in morphometric vertebral fractures, with a RR of 0.53 (95% CI 0.43 to 0.65, p=0.0000). No heterogeneity was detected (p = 0.9980, $I^2 = 0.00\%$).

***Table 3.5:*** *Results details - biphosphonate - alendronate*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***alendronate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.54 | [0.44;0.66] | 0.0000 | 0.9861 ($I^2$=0.00) | 5 | 7475 |
| clinical vertebral fractures | RR=0.45 | [0.28;0.74] | 0.0000 | 1.0000 ($I^2$=0.00) | 1 | 2027 |
| hip fractures | RR=0.62 | [0.41;0.96] | 0.0335 | 0.7601 ($I^2$=0.00) | 5 | 9481 |
| non vertebral fractures | RR=0.82 | [0.72;0.94] | 0.0033 | 0.3728 ($I^2$=0.07) | 6 | 9840 |
| 1-year vertebral fracture | RR=1.03 | [0.02;50.43] | 0.9868 | 1.0000 ($I^2$=0.00) | 1 | 61 |
| 1-year non vertebral fracture | RR=0.52 | [0.30;0.89] | 0.0181 | 1.0000 ($I^2$=0.00) | 1 | 1908 |
| morphometric vertebral fractures | RR=0.53 | [0.43;0.65] | 0.0000 | 0.9980 ($I^2$=0.00) | 3 | 7042 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 3.1:*** *Forest's plot for vertebral fractures*

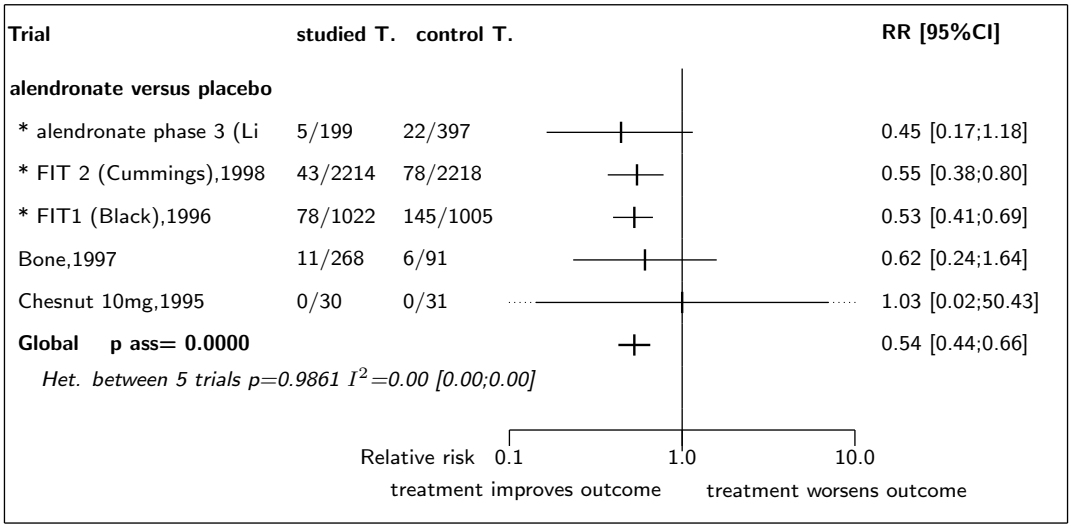


***Figure 3.2:*** *Forest's plot for clinical vertebral fractures*

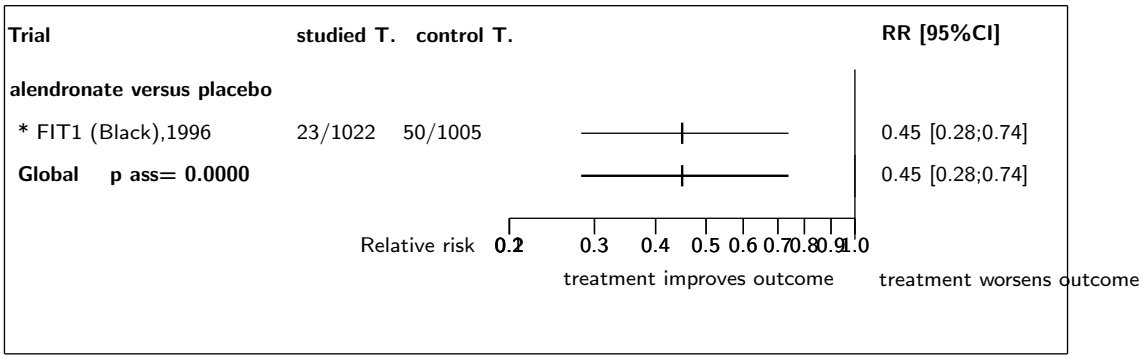



***Figure 3.3:*** *Forest's plot for hip fractures*

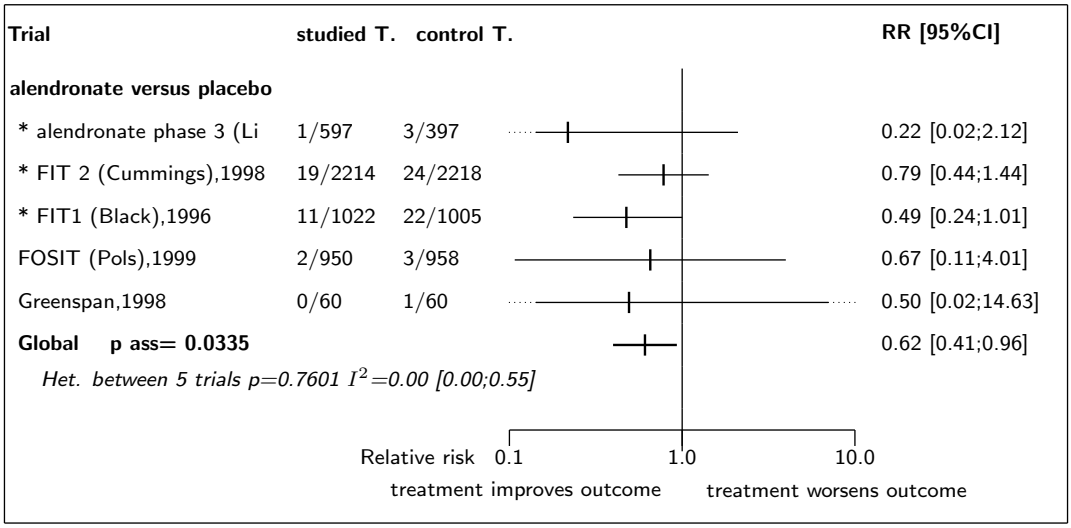


***Figure 3.4:*** *Forest's plot for non vertebral fractures*

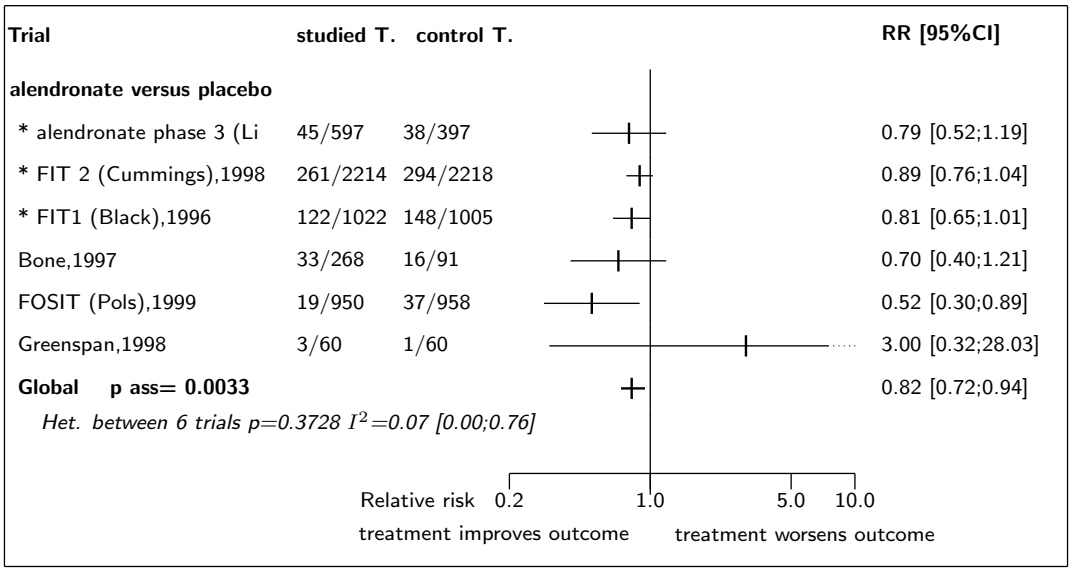



***Figure 3.5:*** *Forest's plot for 1-year vertebral fracture*

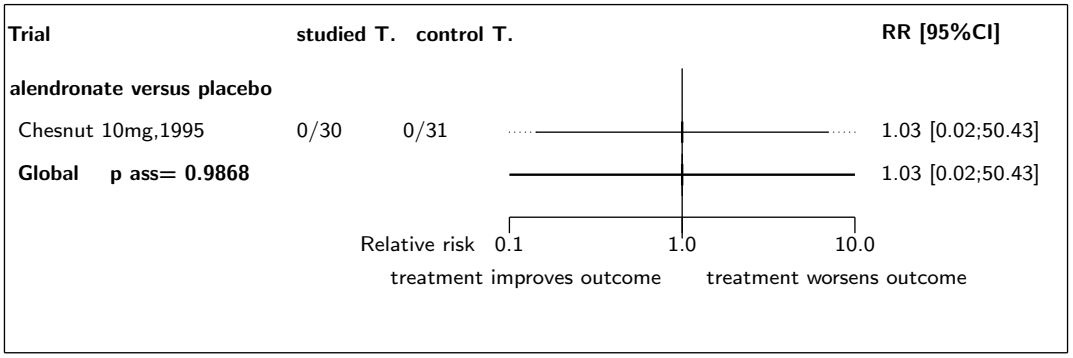



***Figure 3.6:*** *Forest's plot for 1-year non vertebral fracture*

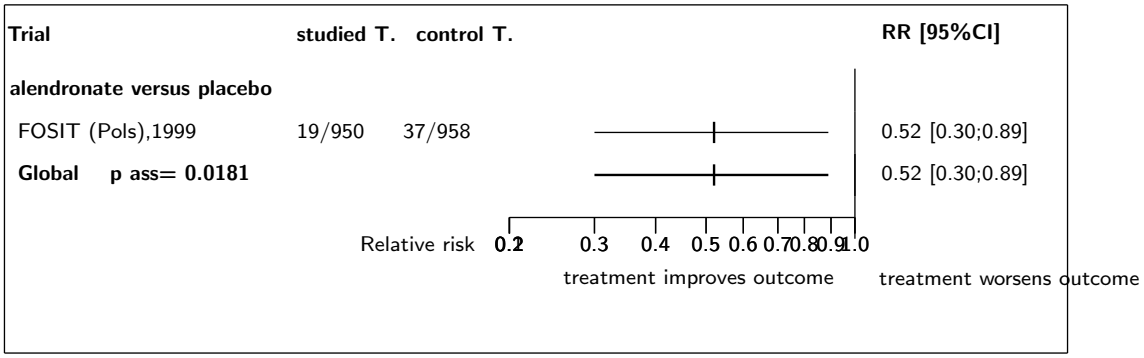
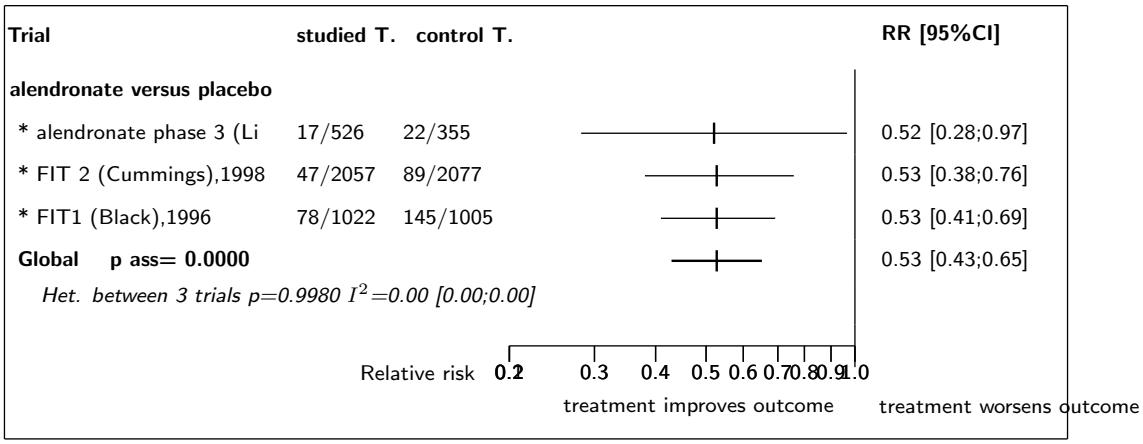


***Figure 3.7:*** *Forest's plot for morphometric vertebral fractures*

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## 3.3 Individual trial summaries

***Table 3.6:*** ** alendronate phase 3 (Liberman), 1995 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=994 (597 vs. 397)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>USA, Australia, Canada, Europe, Israel, Mexico, NZ, SA, multicenter | Women with postmenopausal osteoporosis<br>**Inclusion criteria:** 45 to 80 years old; postmenopausal ( >=5 years since menopause); osteoporosis (defined as a bone mineral density of the lumbar spine that was at least 2.5 SD below the mean value in premenopausal white women)<br>**Exclusion criteria:** other causes of osteoporosis (e.g., treatment with glucocorticoids) or other disorders of bone and mineral metabolism (e.g., vitamin D deficiency, Pagets disease, or hyperparathyroidism); active peptic ulcer disease; abnormal renal function; abnormal hepatic function; abnormalities of the lumbar spine precluding the assessment of bone mineral density at a minimum of three lumbar vertebrae or a history of hip fracture; any prior treatment with bisphosphonates or treatment within the preceding 12 months with estrogen, progestin, calcitonin, fluoride, or an anabolic steroid. | **Studied treatment:** alendronate (5 or 10 mg daily for three years, or 20 mg for two years followed by 5 mg for one year<br>**Control treatment:** placebo<br>**Concomittant treat.:**500mg of calcium daily | Vertebral fractures<br>RR=0.45 [0.17;1.18]<br>Hip fractures<br>RR=0.22 [0.02;2.12]<br>Non vertebral fractures<br>RR=0.79 [0.52;1.19]<br>(table 3)<br>Morphometric vertebral fractures<br>RR=0.52 [0.28;0.97]<br>(table 2, new vertebral frct) |

**Reference**

Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437-43 [PMID=7477143]

***Table 3.7:*** ** FIT 2 (Cummings), 1998 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=4432 (2214 vs. 2218)<br>**Follow-up duration:** 4 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Confirmatory trial at low risk of bias<br>USA, 11 centres<br>**Inclusion period:** NA | Women aged 54 to 81 years with a femoral neck BMD of 0.68 g/cm2 or less (Hologic) but no vertebral fracture<br>**Exclusion criteria:** recent peptic ulcers or ulcers that required hospitalization, dyspepsia requiring daily treatment, significant renal or hepatic dysfunction, medical problems that precluded 3 years of participation, severe malabsorption, blood pressure exceeding 210 mm Hg systolic or 105 mm Hg diastolic, myocardial infarction within 6 months, unstable angina, hypothyroidism, hyperthyroidism, or hyperparathyroidism; estrogen or calcitonin within the preceding 6 months or bisphosphonates or sodium fluoride ( >1 mg/d) at any time | **Studied treatment:** 5 mg/d of alendronate sodium for 2 years followed by 10 mg/d for the remainder of the trial<br>**Control treatment:** placebo | Vertebral fractures<br>RR=0.55 [0.38;0.80]<br>(table 2 may be clinical)<br>Hip fractures<br>RR=0.79 [0.44;1.44]<br>(clinical hip fracture)<br>Non vertebral fractures<br>RR=0.89 [0.76;1.04]<br>Morphometric vertebral fractures<br>RR=0.53 [0.38;0.76]<br>(footnote table 2) |

**Reference**

Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82 [PMID=9875874]

***Table 3.8:*** ** FIT1 (Black), 1996 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=2027 (1022 vs. 1005)<br><br>**Follow-up duration:** 3 years<br><br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br><br>Confirmatory trial at low risk of bias<br><br>USA, multicentre | Women aged 55-81 with low femoral-neck BMD with at least one vertebral fracture<br><br>**Inclusion criteria:** women aged between 55 and 81 years; postmenopausal for at least 2 years; femoral neck BMD of 068 g/cm2 or less (QDR-2000 Hologic, Waltham, MA, USA), about 21 SDs below peak bone mass based on the manufacturers normative data; at least one vertebral fracture at baseline<br><br>**Exclusion criteria:** peptic-ulcer disease (a single hospital admission for uppergastrointestinal bleeding or two or more documented ulcers within the preceding 5 years), dyspepsia requiring daily treatment, abnormal renal function (serum creatinine >144 mol/L), major medical problems that would be likely to preclude participation for 3 years, severe malabsorption syndrome, uncontrolled hypertension (blood pressure >210 mm Hg systolic or >105 mm Hg diastolic), myocardial infarction during the previous 6 months, unstable angina, or evidence of disturbed thyroid or parathyroid f | **Studied treatment:** alendronate (initially 5 mg daily) was increased (to 10 mg daily) at 24 months<br><br>**Control treatment:** placebo | Vertebral fractures<br>RR=0.53 [0.41;0.69]<br>(table 2 (morphometric fractures))<br><br>Clinical vertebral fractures<br>RR=0.45 [0.28;0.74]<br>(table 2)<br><br>Hip fractures<br>RR=0.49 [0.24;1.01]<br>(table 3)<br><br>Non vertebral fractures<br>RR=0.81 [0.65;1.01]<br>(table)<br><br>Morphometric vertebral fractures<br>RR=0.53 [0.41;0.69]<br>(tabe 2) |

**Reference**

Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41 [PMID=8950879]

***Table 3.9:*** *Adami, 1995 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=211 (140 vs. 71)<br>**Follow-up duration:** 2 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>Italy, 9 centres | Postmenopausal women between the ages of 48 and 76 with spinal bone mineral density >or = 2 SD below adult mean peak in the two-year<br>**Inclusion criteria:** women between the ages of 48 and 76 years; at least 2 years past natural menopause; lumbar spine bone mineraldensity (BMD) >2 SD below the mean for youngpremenopausal women<br>**Exclusion criteria:** any secondary cause of osteoporosis, other metabolic bone disease, hyper- or hypothyrodism or any associated health problems taht could affect tehir participation in teh study | **Studied treatment:** alendronate 10 or 20 mg/day<br>**Control treatment:** placebo<br>**Concomittant treat.:**calcium 500mg daily<br>**note:** 4 arms: alendronate 10 mg/day, alendronate 20 mg/day, or open-label intranasal salmon calcitonin 100 IU/day; placebo | |

**Reference**

Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, Gandolini G, Gnessi L, Laurenzi M, Lombardi A. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. Bone 1995;17:383-90 [PMID=8573412]

***Table 3.10:*** *Bone, 1997 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=359 (268 vs. 91)<br>**Follow-up duration:** 2 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>USA, 15 centres | Women with lumbar spine BMD at least 2.0 SD below the peak young adult mean<br>**Inclusion criteria:** good health apart from osteoporosis; lumbar spine BMD of 0.824 g/cm2 or less byHologic DXA or 0.944 g/cm2 or less by Lunar DXA (2.0 sd below mean peak levels);<br>**Exclusion criteria:** more than 1 lumbar crush fracture; spinal anatomy was otherwise unsuitable for DXA analysis; history of recent major gastrointestinal disease, such as peptic ulcer, esophageal disorder, or malabsorption, or had recently used a drug to inhibit gastric acid secretion for more than 2 weeks; chronic nonsteroidal antiinflammatory therapy or agents known to affect bone metabolism (such as etidronate, estrogen, glucocorticoids, fluoride, or calcitonin) | **Studied treatment:** 1.0, 2.5, or 5.0 mg alendronate daily<br>**Control treatment:** placebo<br>**Concomittant treat.:**calcium supplementcontaining 500 mg elemental calcium | Vertebral fractures<br>RR=0.62 [0.24;1.64]<br>(text p270)<br>Non vertebral fractures<br>RR=0.70 [0.40;1.21]<br>(clinical) |

**Reference**

Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein RS, Licata AA, McClung MR, Kimmel DB, Gertz BJ, Hale E, Polvino WJ. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab 1997;82:265-74 [PMID=8989272]

***Table 3.11:*** *Chesnut 10mg, 1995 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=61 (30 vs. 31)<br>**Follow-up duration:** 2 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>USA, 7 centres | Postmenopausal women, aged 42 to 75 years, with low bone mineral density of the lumbar spine<br>**Inclusion criteria:** healthy women aged 42 to 75 years; postmenopausal, with lumbar spine BMD <=0.88 g/cm2 (approximately 2 standard deviations below young, normal US white female mean BMD values)<br>**Exclusion criteria:** spine or hip fractures attribuable to osteoporosis | **Studied treatment:** alendronate 10 mg daily for 2 years<br>**Control treatment:** placebo<br>**Concomittant treat.:**500mg of elemental calcium<br>**note:** 6 arms: placebo or 5 or 10 mg of alendronate, for 24 months; a fourth group received 40 mg of alendronate for 3 fourth group received 40 mg of alendronate for 3 months, followed by 2.5 mg for 21 months. The last 2 groups received 20 or 40 mg of alendronate for 12 months followed by placebo for 12 months. | |

**Reference**

Chesnut CH 3rd, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, Singer FR, Stock JL, Yood RA, Delmas PD. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. Am J Med 1995;99:144-52 [PMID=7625419]

***Table 3.12:*** *FOSIT (Pols), 1999 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=1908 (950 vs. 958)<br>**Follow-up duration:** 1 year<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>34 countries, 153 centres | Postmenopausal women with lumbar spine BMD 2 standard deviations or more below the premenopausal adult mean<br>**Inclusion criteria:** postmenopausal for at least 3 years; not older than 85 years; BMD of the lumbar spine (L24) at least 2 standard deviations (SD) below the mean for mature, premenopausal women; good health and between 20% below and 50% above ideal body weight as defined in the Metropolitan Life Insurance Company Height and Weight Table<br>**Exclusion criteria:** metabolic bone disease other than postmenopausal osteoporosis; disturbed parathyroid or thyroid function; major gastrointestinal disease within the year before enrollment or use of a drug to inhibit gastric acid secretion for >2 weeks within 3 months of study entry; myocardial infarction within the year prior to enrollment; uncontrolled hypertension or untreated angina; significantly impaired renal function (serum creatinine >150 mmol/l); evidence of significant end organ disease | **Studied treatment:** oral alendronate 10 mg for 12 months<br>**Control treatment:** placebo<br>**Concomittant treat.:**elemental calcium 500mg daily | Hip fractures<br>RR=0.67 [0.11;4.01]<br>Non vertebral fractures<br>RR=0.52 [0.30;0.89]<br>1-year non vertebral fracture<br>RR=0.52 [0.30;0.89] |

**Reference**

Pols HA, Felsenberg D, Hanley DA, Stepn J, Muoz-Torres M, Wilkin TJ, Qin-sheng G, Galich AM, Vandormael K, Yates AJ, Stych B. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9:461-8 [PMID=10550467]

***Table 3.13:*** *Greenspan, 1998 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=120 (60 vs. 60)<br>**Follow-up duration:** 2.5 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>USA, single center | Community-dwelling, ambulatory women 65 years of age and older<br>**Inclusion criteria:** no BMD criteria<br>**Exclusion criteria:** history of any illness affecting bone and mineral metabolism (e.g., renal failure, hepatic failure, active malignancy, current hyperthyroidism or hyperparathyroidism, or malabsorption); medications known to affect bone metabolism (e.g., glucocorticoids, anticonvulsants); treatement for osteoporosis with bisphosphonates, hormone replacement therapy, or calcitonin within 1 year of screening | **Studied treatment:** alendronate for 2.5 years<br>5 mg daily increased to 101mg daily in November 1993, when data became available thatthe 10 mg dose of alendronate produced greater increasesin bone density than the 5 mg dose<br>**Control treatment:** placebo<br>**Concomittant treat.:**suplemental 250 mg of elemental calcium and 125 IU ofvitamin D to provide a total daily calcium intake of at least1000 mg | Non vertebral fractures<br>RR=3.00 [0.32;28.03] |

**Reference**

Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. J Bone Miner Res 1998;13:1431-8 [PMID=9738515]

# 4 Detailed results for etidronate

## 4.1 Available trials

A total of 3 RCTs which randomized 181 patients were identified: it compared etidronate with control and 2 trials compared etidronate with placebo.
The average study size was 60 patients (range 35 to 80). The first study was published in 1990, and the last study was published in 1998.
A total of 1 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Vertebral fractures data was reported in 2 trials; 1 trials reported data on hip fractures; and 1 trials reported data on non vertebral fractures.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of etidronate.

***Table 4.1:*** *Treatment description - biphosphonate - etidronate*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Etidronate versus control** | | |
| Montessori (1997) [**?**] | intermittent, cyclic etidronate<br>etidronate 400 mg once daily for 14 days followed by 76 days of 500 mg of elementary calcium once daily; this cycle was repeated every 3 months | calcium alone<br>500 mg of elementary calcium once daily |
| **Etidronate versus placebo** | | |
| Storm (1990) [**?**] | intermittent cyclical etidronate 400mg daily for 2 weeks followed by a 13-week period with no drugs, for 150 weeks<br>**Concomittant treatment:** daily supplements of elemental calcium (500mg) and a multi-vitamin containing 400IU of vit D throughout the 15-week study cycle | placebo |
| Wimalawansa (1998) [**?**] [b] | combined HRT plus etidronate<br>intermittent cyclical etidronate for 4 years<br>400 mg disodium etidronate orally (5 to 10 mg/kg per day) daily for 14 days (intermittent cyclically administered etidronate every 12 weeks)<br>**Concomittant treatment:** 1.0 g elemental calcium and400 units vitamin D per day | control |

b) 4 arms: control, cyclical estrogen and progesterone, intermittent cyclical etidronate, both HRT and etidronate

***Table 4.2:*** *Descriptions of participants - biphosphonate - etidronate*

| Trial | Patients |
|---|---|
| **Etidronate versus control** | |

continued...

| Trial | Patients | |
|---|---|---|
| Montessori (1997) [?] | Osteoporotic postmenopausal women with or without fractures | |
| | **Inclusion criteria:** asymptomatic women less than 75 years old who had been amenorrhoeic for at least 1 year; to be ambulant; bone mineral density (BMD) of the lumbar spine >1 SD below that of age matched controls (Z-score <-1 SD). | **Exclusion criteria:** systematic treatment with oestrogens, androgens, vitamin D, calclium in pharmacological doses ( >1g/day), calcitonin or other bisphosphonates in the preceding year; secondary osteoporosis;metabolic bone disease; active gastrointestinal or liver disease; renal disease (serum creatinine >115 micromol/l); active cancer within the last 3 years; alcoholism |
| **Etidronate versus placebo** | | |
| Storm (1990) [?] | Women with postmenopausal osteoporosis | |
| | **Inclusion criteria:** evidence of osteoporosis determined by teh presence of at least but not more tahn 4 atraumatic vertebral crush fracture and radiographically proved demineralization of vertebrae | **Exclusion criteria:** secondary causes of osetoporosis; Paget's disease of bone, renal osteodystrophy; impairment of renal, cardiac, or thyroid function; history of therapy with corticosteroids, estrogens, calcitonin, calcium or vitamin D for 3 months or more during the 6 months the study entry; fluoride or diphosphonate theray for any disease |
| Wimalawansa (1998) [?] | Postmenopausal women with established osteoporosis | |
| | **Inclusion criteria:** evidence of osteoporosis as determined by at least 1 (but not more than 4) radiographically demonstrable atraumatic thoracic vertebral crush fractures, and spine BMD 2.0 standard deviations below the reference | **Exclusion criteria:** surgical menopause (ie, oophorectomy), secondary osteoporosis, or other medical conditions that can affect the skeleton, or were taking medications that affect calcium metabolism within the previous 3 years were excluded from this study; treatment with HRT, anabolic steroids, glucocorticoids, calcitonin, fluoride, or bisphosphonates at any time since menopause |

***Table 4.3:*** *Main patients characteristics - biphosphonate - etidronate*

| Trial | Characteristics |
|---|---|
| **Etidronate versus control** | |
| Montessori, 1997 [?] | age (yr): 62.5 yr<br>time since menopause (yr): 15.1 yr<br>low BMD as inclusion criteria: <-1 SD<br>low BMD as criteria: yes ( <-1 SD)<br>prevalent fracture as criteria: no<br>inclusion without BMD: no<br>prevalente fracture at baseline: yes or not |
| **Etidronate versus placebo** | |
| Storm, 1990 [?] | age (yr): 68.35 y<br>time since menopause (yr): 21.55 y |
| Wimalawansa, 1998 [?] | age (yr): 64.9 y<br>time since menopause (yr): 14.9 y<br>BMD: 0.82 g/cm2 |

***Table 4.4:*** *Design and methodological quality of trials - biphosphonate - etidronate*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Etidronate versus control** | | | | |
| Montessori, 1997 [?] n=80 | Cross over open exploratory trial | 3 years inclusion period: feb 1991 - feb 1992 | The Netherlands 2 centres | not defined |
| **Etidronate versus placebo** | | | | |
| Storm, 1990 [?] n=66 | Parallel groups double-blind exploratory trial | 2.9 years inclusion period: oct 1983 - apr 1986 | Denmark single center | |
| Wimalawansa, 1998 [?] n=35 | Parallel groups open exploratory trial | 4 years | | NA |

## 4.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Etidronate versus control

The single study eligible for this comparison provided data on **vertebral fractures**. There was no statistically significant difference in vertebral fractures between etidronate and control, with a RR of 0.15 (95%CI 0.01 to 2.95, p=0.2137) in favour of etidronate. In other words, vertebral fractures was slightly lower in the etidronate group , but this was not statistically significant.

### Etidronate versus placebo

Only one of the 2 studies eligible for this comparison provided data on **vertebral fractures**. There was no statistically significant difference in vertebral fractures between etidronate and placebo, with a RR of 0.64 (95%CI 0.18 to 2.26, p=0.4834) in favour of etidronate. In other words, vertebral fractures was slightly lower in the etidronate group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **hip fractures**. No statistically significant difference between the groups was found in hip fractures, with a RR of 0.50 (95% CI 0.05 to 5.25, p=0.5634).
Only one of the 2 studies eligible for this comparison provided data on **non vertebral fractures**. No statistically significant difference between the groups was found in non vertebral fractures, with a RR of 0.83 (95% CI 0.28 to 2.46, p=0.7417).

***Table 4.5:*** *Results details - biphosphonate - etidronate*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***etidronate versus control*** | | | | | | |
| vertebral fractures | RR=0.15 | [0.01;2.95] | 0.2137 | 1.0000 ($I^2$=0.00) | 1 | 71 |
| ***etidronate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.64 | [0.18;2.26] | 0.4834 | 1.0000 ($I^2$=0.00) | 1 | 35 |

continued...

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| hip fractures | RR=0.50 | [0.05;5.25] | 0.5634 | 1.0000 ($I^2$=0.00) | 1 | 66 |
| non vertebral fractures | RR=0.83 | [0.28;2.46] | 0.7417 | 1.0000 ($I^2$=0.00) | 1 | 66 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 4.1:*** *Forest's plot for vertebral fractures*

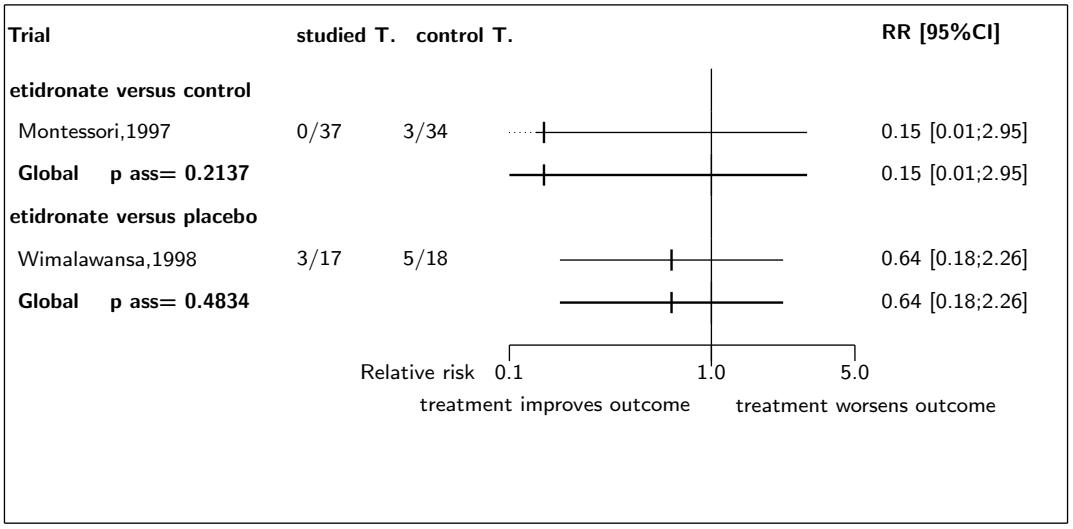



***Figure 4.2:*** *Forest's plot for hip fractures*

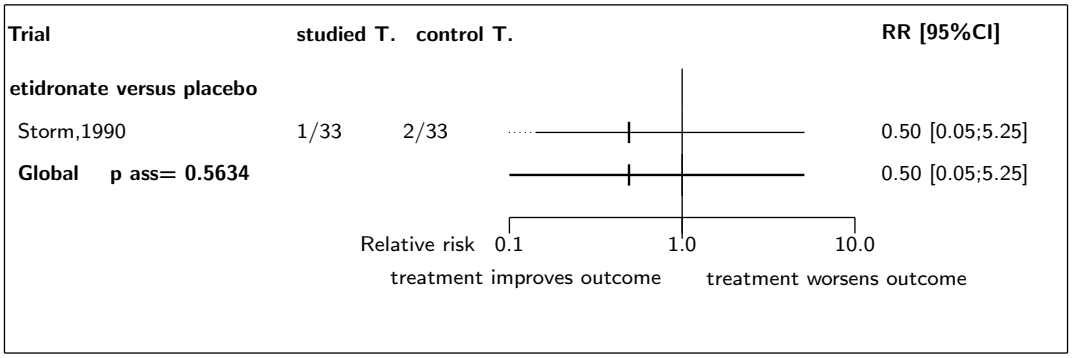
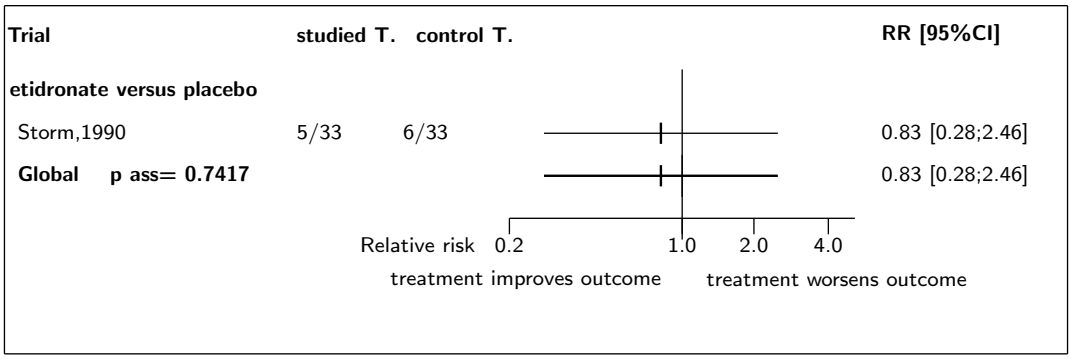


***Figure 4.3:*** *Forest's plot for non vertebral fractures*




# References

[1] Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker K. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporos Int 1997;7:52-8. [PMID=9102064]

[2] Storm T, Thamsborg G, Steiniche T, Genant HK, Srensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322:1265-71. [PMID=2109197]

[3] Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 1998;104:219-26. [PMID=9552083]

## 4.3 Individual trial summaries

***Table 4.6:*** *Montessori, 1997 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=80 (40 vs. 40)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Cross over<br>Open<br>Exploratory trial<br>The Netherlands, 2 centres<br>**Inclusion period:** feb 1991 - feb 1992 | Osteoporotic postmenopausal women with or without fractures<br>**Inclusion criteria:** asymptomatic women less than 75 years old who had been amenorrhoeic for at least 1 year; to be ambulant; bone mineral density (BMD) of the lumbar spine >1 SD below that of age matched controls (Z-score <-1 SD).<br>**Exclusion criteria:** systematic treatment with oestrogens, androgens, vitamin D, calclium in pharmacological doses ( >1g/day), calcitonin or other bisphosphonates in the preceding year; secondary osteoporosis;metabolic bone disease; active gastrointestinal or liver disease; renal disease (serum creatinine >115 micromol/l); active cancer within the last 3 years; alcoholism | **Studied treatment:** intermittent, cyclic etidronate<br>etidronate 400 mg once daily for 14 days followed by 76 days of 500 mg of elementary calcium once daily; this cycle was repeated every 3 months<br>**Control treatment:** calcium alone 500 mg of elementary calcium once daily | |

**Reference**

Montessori ML, Scheele WH, Netelenbos JC, Kerkhoff JF, Bakker K. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporos Int 1997;7:52-8 [PMID=9102064]

***Table 4.7:*** *Storm, 1990 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=66 (33 vs. 33)<br>**Follow-up duration:** 2.9 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>Denmark, single center<br>**Inclusion period:** oct 1983 - apr 1986 | Women with postmenopausal osteoporosis<br>**Inclusion criteria:** evidence of osteoporosis determined by teh presence of at least but not more tahn 4 atraumatic vertebral crush fracture and radiographically proved demineralization of vertebrae<br>**Exclusion criteria:** secondary causes of osetoporosis; Paget's disease of bone, renal osteodystrophy; impairment of renal, cardiac, or thyroid function; history of therapy with corticosteroids, estrogens, calcitonin, calcium or vitamin D for 3 months or more during the 6 months the study entry; fluoride or diphosphonate theray for any disease | **Studied treatment:** intermittent cyclical etidronate 400mg daily for 2 weeks followed by a 13-week period with no drugs, for 150 weeks<br>**Control treatment:** placebo<br>**Concomittant treat.:**daily supplements of elemental calcium (500mg) and a multivitamin containing 400IU of vit D throughout the 15-week study cycle | Hip fractures<br>RR=0.50 [0.05;5.25]<br>Non vertebral fractures<br>RR=0.83 [0.28;2.46] |

**Reference**

Storm T, Thamsborg G, Steiniche T, Genant HK, Srensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322:1265-71 [PMID=2109197]

***Table 4.8:*** *Wimalawansa, 1998 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=35 (17 vs. 18)<br>**Follow-up duration:** 4 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Open<br>Exploratory trial | Postmenopausal women with established osteoporosis<br>**Inclusion criteria:** evidence of osteoporosis as determined by at least 1 (but not more than 4) radiographically demonstrable atraumatic thoracic vertebral crush fractures, and spine BMD 2.0 standard deviations below the reference<br>**Exclusion criteria:** surgical menopause (ie, oophorectomy), secondary osteoporosis, or other medical conditions that can affect the skeleton, or were taking medications that affect calcium metabolism within the previous 3 years were excluded from this study; treatment with HRT, anabolic steroids, glucocorticoids, calcitonin, fluoride, or bisphosphonates at any time since menopause | **Studied treatment:** combined HRT plus etidronate intermittent cyclical etidronate for 4 years<br>400 mg disodium etidronate orally (5 to 10 mg/kg per day) daily for 14 days (intermittent cyclically administered etidronate every 12 weeks)<br>**Control treatment:** control<br>**Concomittant treat.:**1.0 g elemental calcium and400 units vitamin D per day<br>**note:** 4 arms: control, cyclical estrogen and progesterone, intermittent cyclical etidronate, both HRT and etidronate | Vertebral fractures<br>RR=0.64 [0.18;2.26]<br>(new vertebral fracture table 2) |

**Reference**

Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 1998;104:219-26 [PMID=9552083]

# 5 Detailed results for ibandronate

## 5.1 Available trials

Only one trial which randomized 1964 patients was identified: it compared ibandronate with placebo.
This trial included 1964 patients and was published in 2005.
This trial was double blind in design.
It was reported in English language.
1-year vertebral fracture data was reported in 1 trials; 1 trials reported data on major non vertebral fractures; 1 trials reported data on morphometric vertebral fractures; 1 trials reported data on non vertebral fractures; and 1 trials reported data on hip fractures.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of ibandronate.

***Table 5.1:*** *Treatment description - biphosphonate - ibandronate*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Ibandronate versus placebo** | | |
| * BONE (Chesnut) daily ibandronate (2005) [**?**] [a] | oral daily ibandronate (2.5 mg) | placebo |

a) 3 arms: daily or oral intermittent ibandronate, placebo

***Table 5.2:*** *Descriptions of participants - biphosphonate - ibandronate*

| Trial | Patients | |
|---|---|---|
| **Ibandronate versus placebo** | | |
| * BONE (Chesnut) daily ibandronate (2005) [**?**] | Postmenopausal women (age 55 years-80 years; >or = 5 years since menopause) with osteoporosis (low lumbar spine bone mineral density and one to four prevalent vertebral fractures [T4-L4]). | |
| | **Inclusion criteria:** postmenopausal-women (aged 55 years80 years; time since menopause:at least 5 years) with osteoporosis (one to four prevalentvertebral fractures [T4L4] and BMD T-score 2 to 5in at least one vertebra [L1L4]) | **Exclusion criteria:** |

***Table 5.3:*** *Main patients characteristics - biphosphonate - ibandronate*

| Trial | Characteristics |
|---|---|
| **Ibandronate versus placebo** | |
| * BONE (Chesnut) daily ibandronate, 2005 [**?**] | age (yr): 68.8 y<br>prevalent fractures (%): 1.6%<br>time since menopause (yr): 20.8 yr<br>t-score (lumbar): -2.8<br>low BMD as inclusion criteria: between -5 and -2 SD<br>low BMD as criteria: yes<br>prevalent fracture as criteria: yes<br>inclusion without BMD: no<br>prevalente fracture at baseline: 1.6% |

***Table 5.4:*** *Design and methodological quality of trials - biphosphonate - ibandronate*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Ibandronate versus placebo** | | | | |
| * BONE (Chesnut) daily ibandronate, 2005 [**?**] n=1964 | Parallel groups double-blind confirmatory trial at low risk of bias | 3 years | USA, Canada, Europe 73 centres | morphometric vertebral fractures |

## 5.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Ibandronate versus placebo

The single study eligible for this comparison provided data on **hip fractures**. No statistically significant difference between the groups was found in hip fractures, with a RR of 0.67 (95% CI 0.19 to 2.35, p=0.5268).
The single study eligible for this comparison provided data on **major non vertebral fractures**. No statistically significant difference between the groups was found in major non vertebral fractures, with a RR of 1.14 (95% CI 0.82 to 1.57, p=0.4360).
The single study eligible for this comparison provided data on **non vertebral fractures**. No statistically significant difference between the groups was found in non vertebral fractures, with a RR of 1.14 (95% CI 0.82 to 1.57, p=0.4360).
The single study eligible for this comparison provided data on **1-year vertebral fracture**. No statistically significant difference between the groups was found in 1-year vertebral fracture, with a RR of 0.62 (95% CI 0.28 to 1.37, p=0.2386).
The single study eligible for this comparison provided data on **morphometric vertebral fractures**. The analysis detected a statistically significant difference in favor of ibandronate in morphometric vertebral fractures, with a RR of 0.51 (95% CI 0.34 to 0.74, p=0.0000).

***Table 5.5:*** *Results details - biphosphonate - ibandronate*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***ibandronate versus placebo*** | | | | | | |
| hip fractures | RR=0.67 | [0.19;2.35] | 0.5268 | 1.0000 ($I^2$=0.00) | 1 | 1952 |
| major non vertebral fractures | RR=1.14 | [0.82;1.57] | 0.4360 | 1.0000 ($I^2$=0.00) | 1 | 1952 |
| non vertebral fractures | RR=1.14 | [0.82;1.57] | 0.4360 | 1.0000 ($I^2$=0.00) | 1 | 1952 |
| 1-year vertebral fracture | RR=0.62 | [0.28;1.37] | 0.2386 | 1.0000 ($I^2$=0.00) | 1 | 1952 |
| morphometric vertebral fractures | RR=0.51 | [0.34;0.74] | 0.0000 | 1.0000 ($I^2$=0.00) | 1 | 1952 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 5.1:*** *Forest's plot for hip fractures*

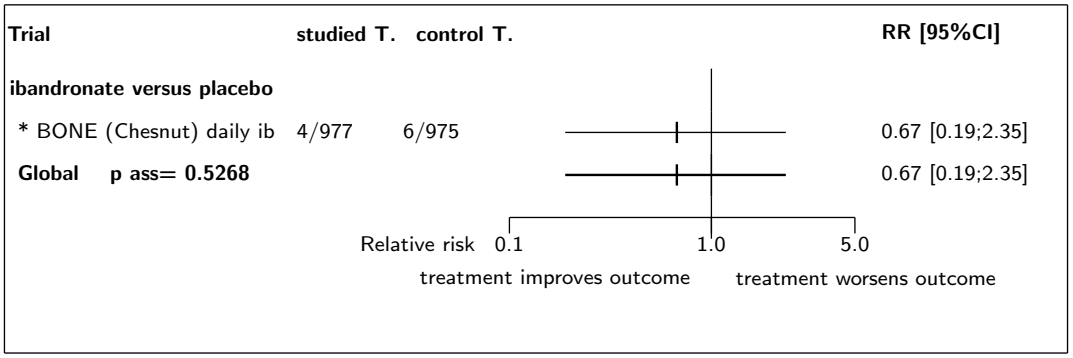



***Figure 5.2:*** *Forest's plot for major non vertebral fractures*

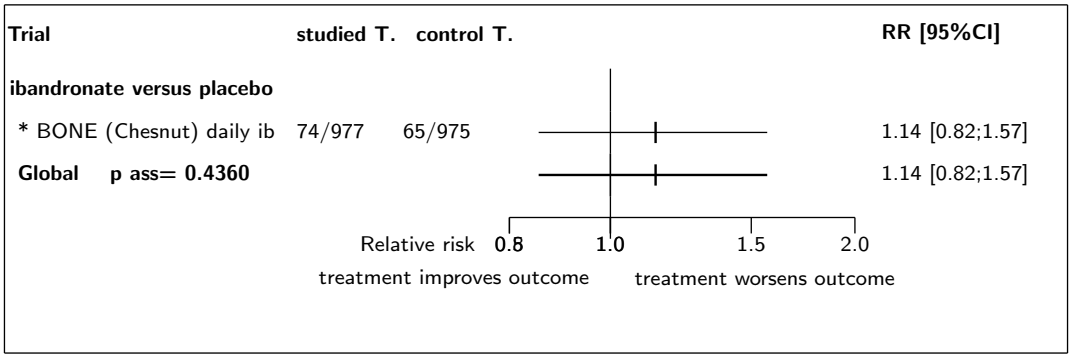


***Figure 5.3:*** *Forest's plot for non vertebral fractures*

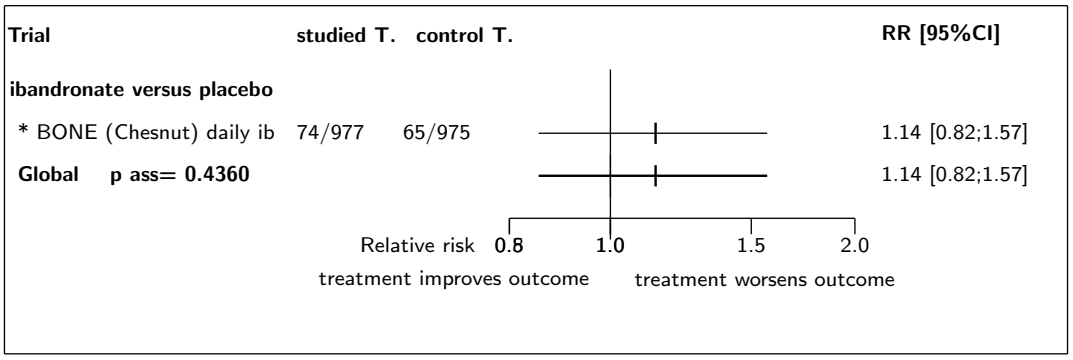



***Figure 5.4:*** *Forest's plot for 1-year vertebral fracture*

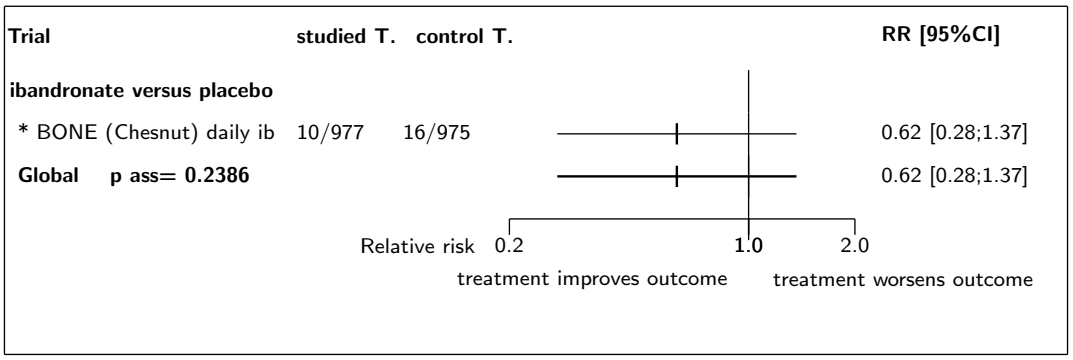
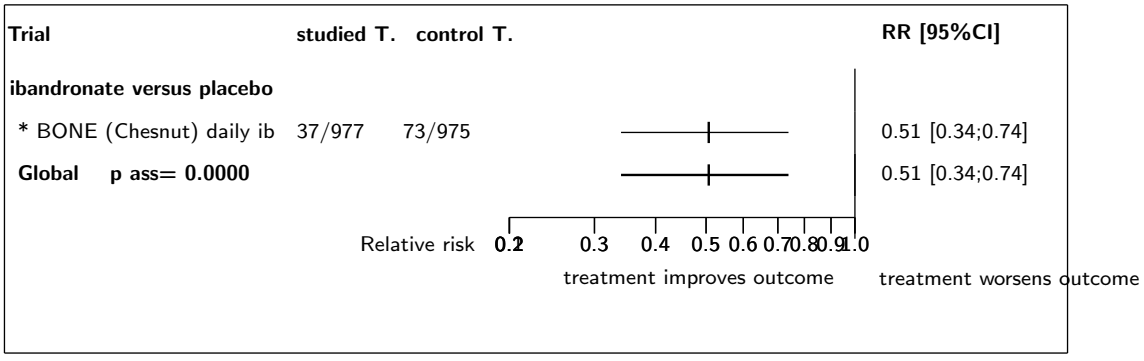



***Figure 5.5:*** *Forest's plot for morphometric vertebral fractures*



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[1] Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, Wasnich RD, Watts NB, Schimmer RC, Recker RR. Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. Curr Med Res Opin 2005;21:391-401. [PMID=15811208]

## 5.3 Individual trial summaries

***Table 5.6:*** ** BONE (Chesnut) daily ibandronate, 2005 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=1964 (982 vs. 982)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Confirmatory trial at low risk of bias<br>USA, Canada, Europe, 73 centres | Postmenopausal women (age 55 years-80 years; >or = 5 years since menopause) with osteoporosis (low lumbar spine bone mineral density and one to four prevalent vertebral fractures [T4-L4]).<br>**Inclusion criteria:** postmenopausalwomen (aged 55 years80 years; time since menopause:at least 5 years) with osteoporosis (one to four prevalentvertebral fractures [T4L4] and BMD T-score 2 to 5in at least one vertebra [L1L4]) | **Studied treatment:** oral daily ibandronate (2.5 mg)<br>**Control treatment:** placebo<br>**note:** 3 arms: daily or oral intermittent ibandronate, placebo | Hip fractures<br>RR=0.67 [0.19;2.35]<br>(FDA pg 25)<br>Major non vertebral fractures<br>RR=1.14 [0.82;1.57]<br>(clinical osteoP frct, FDA, pg 25)<br>Non vertebral fractures<br>RR=1.14 [0.82;1.57]<br>(clinical osteoP frct, FDA, pg 25)<br>1-year vertebral fracture<br>RR=0.62 [0.28;1.37]<br>(morphoM, FDA, pg 21)<br>Morphometric vertebral fractures<br>RR=0.51 [0.34;0.74]<br>(new morphoM vertebral frct, FDA P3 pg 21, 3 year) |

**Reference**

Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, Wasnich RD, Watts NB, Schimmer RC, Recker RR. Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. Curr Med Res Opin 2005;21:391-401 [PMID=15811208]

# 6 Detailed results for risedronate

## 6.1 Available trials

A total of 6 RCTs which randomized 13101 patients were identified: all compared risedronate with placebo.
The average study size was 2183 patients (range 132 to 9331). The first study was published in 1997, and the last study was published in 2001.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Non vertebral fractures data was reported in 5 trials; 4 trials reported data on vertebral fractures; 3 trials reported data on hip fractures; 2 trials reported data on 1-year vertebral fracture; 2 trials reported data on major non vertebral fractures; and 1 trials reported data on morphometric vertebral fractures.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of risedronate.

***Table 6.1:*** *Treatment description - biphosphonate - risedronate*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Risedronate versus placebo** | | |
| * VERT (Harris) 5 mg (1999) [**?**] [a] | oral treatment for 3 years with risedronate 5 mg/d<br>**Concomittant treatment:** calcium supplement equivalent to 1000 mg of elemental calcium daily, to be taken with the evening meal. Subjects with low serum 25-hydroxyvitamin D levels at baseline (,40 nmol/L) also received cholecalciferol supplementation (up to 500 IU/d) | placebo |
| * VERT europe (Reginster) 5mg (2000) [**?**] [b] | risedronate 5 mg/day for 3 years<br>**Concomittant treatment:** All patients received calcium 1000 mg/dayin a single dose with lunch or the evening meal and up to500 IU/day vitamin D if baseline 25-hydroxyvitamin Dlevels were below 40 nmol/l | placebo |
| BMD-MN (Fogelman) (2000) [**?**] [c] | Risedronate 2.5 mg/d or risedronate 5 mg/d<br>**Concomittant treatment:** dairy or other calcium-containing products at the same time as studymedication; elemental calcium (1g/day), as calcium carbonate, at a different time of day from the studydrug, preferably with food | placebo |
| Clemmesen (1997) [**?**] [d] | 2.5 mg continuous risedronate or 2.5 mg cyclic risedronate for 2 years<br>cyclic risedronate = 2.5 mg daily risedronate for 2 weeksfollowed by 10 weeks on placebo<br>**Concomittant treatment:** calcium supplement 1 g daily | placebo |
| McClung (overall) (2001) [**?**] [e] | oral risedronate (2.5 or 5.0 mg daily) | placebo |
| risedronate dose ranging (McClung) (1999) [**?**] [f] | Risedronate 2.5 mg/d or risedronate 5 mg/d for up to 18 months<br>**Concomittant treatment:** supplemental calcium 1g daily | placebo |

continued...

| Trial | Studied treatment | Control treatment |
|---|---|---|
| a) initially 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d but the 2.5-mgarm was discontinued by protocol amendment (external evidence for less efficacy) b) 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d but 2.5 mggroup was discontinued after 2 years, c) 3 arms: placebo, Risedronate 2.5 mg/d, risedronate 5 mg/d. The 2.5-mg risedronate group was prematurely discontinuedby protocol amendment at 9 of the 13 centers, on the basis ofefficacy and safety assessments from other RCTs d) 3 arms: placebo, 2.5 mg continuous risedronate, 2.5 mg cyclic risedronate e) 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d f) 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d | | |

***Table 6.2:*** *Descriptions of participants - biphosphonate - risedronate*

| Trial | Patients | |
|---|---|---|
| **Risedronate versus placebo** | | |
| * VERT (Harris) 5 mg (1999) [?] | Ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline | |
| | **Inclusion criteria:** no older than 85 years; 5 years had elapsed since natural or surgical menopause; either 2 or more radiographically identified vertebral fractures (T4-L4, inclusive) or 1 vertebral fracture and low lumbar- spine (L1-L4) BMD (defined as <=0.83 g/cm2 [Hologic instrument] or <=0.94 g/cm2 [Lunar instrument]). These values represent a T score of 2 (2 SDs below the mean for young adults). | **Exclusion criteria:** conditions that might interfere with the evaluation of spinal bone loss; drugs known to affect bone metabolism (such as calcitonin, calcitriol or cholecalciferol supplements within 1 month prior to study entry; anabolic steroids, estrogen or estrogen-related drugs, or progestins within 3 months; or bisphosphonates, fluoride, or subcutaneous estrogen implants within 6 months) |
| * VERT europe (Reginster) 5mg (2000) [?] | Postmenopausal women with two or more prevalent vertebral fractures | |
| | **Inclusion criteria:** ambulatory women; up to 85 years old and at least 5 years postmenopausal; at least two radiographically confirmed vertebral (T4L4) fractures | **Exclusion criteria:** conditions thatmight interfere with evaluation of spinal osteoporosis; use of calcitonin, calcitriol or vitamin D supplementswithin 1 month, anabolic steroids, estrogen,estrogen-related drugs or progestogen within 3 months,or bisphosphonates, fluoride or subcutaneous estrogenimplant within 6 months. |
| BMD-MN (Fogelman) (2000) [?] | Postmenopausal women with low bone mass | |
| | **Inclusion criteria:** women up to 80 yr of age; postmenopausal for at least 1 yr, based on the date of theirlast menstrual period; mean lumbar spine (L1L4) T-score of22 or less | **Exclusion criteria:** hyperparathyroidism,hyperthyroidism, or osteomalacia within a year beforethe study; a history of cancer; or abnormalities that would interfere withthe measurement of lumbar spine BMD by dual-energy x-ray absorptiometry; had taken (within612 months, depending on the medication) or were still taking treatment-known to affect bone metabolism, including an injection of vitaminD >= 10,000IU |
| Clemmesen (1997) [?] | Patients with postmenopausal osteoporosis and at least one, but no more than four prevalent vertebral fractures at baseline | |
| | **Inclusion criteria:** otherwise healthypostmenopausal women, 5381 years of age and at least 1 year past the menopause, withestablished postmenopausal osteoporosis defined as atleast one, but no more than four vertebral fractures, andat least three intact lumbar vertebrae. | **Exclusion criteria:** |

continued...

| Trial | Patients |
|---|---|
| McClung (overall) (2001) [?] | Women 70 to 79 years old with osteoporosis and women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck |
| | **Inclusion criteria:** women 70 to 79 years old who had osteoporosis (indicated by a T score for bone mineral density at the femoral neck that was more than 4 SD below the mean peak value in young adults or lower than -3 plus a nonskeletal risk factor for hip fracture, such as poor gait or a propensity to fall) and women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck (T score, lower than -4 or lower than -3 plus a hip-axis length of 11.1 cm or greater) **Exclusion criteria:** |
| risedronate dose ranging (McClung) (1999) [?] | Menopausal women with low BMD (T-score <-2) |

***Table 6.3:*** *Main patients characteristics - biphosphonate - risedronate*

| Trial | Characteristics |
|---|---|
| **Risedronate versus placebo** | |
| * VERT (Harris) 5 mg, 1999 [?] | age (yr): 69 y<br>prevalent fractures (%): 81.3%<br>time since menopause (yr): 24 yr<br>t-score (lumbar): -2.4 (lumbar spine)<br>BMD: 0.597 (femoral neck)<br>prevalente fracture at baseline: 81.3% |
| * VERT europe (Reginster) 5mg, 2000 [?] | age (yr): 71 y<br>prevalent fractures (%): 100%<br>time since menopause (yr): 25 y<br>t-score (lumbar): -2.77<br>BMD: 785 Standardized lumbar spine<br>prevalente fracture at baseline: 100% |
| BMD-MN (Fogelman), 2000 [?] | age (yr): 65 y r<br>prevalent fractures (%): 30%<br>time since menopause (yr): 18 yr<br>t-score (lumbar): -2.90<br>BMD: .740<br>prevalente fracture at baseline: 30% |
| Clemmesen, 1997 [?] | age (yr): 68 y<br>prevalent fractures (%): 100%<br>time since menopause (yr): 20 yr<br>BMD: 0.778 (AS spine)<br>prevalente fracture at baseline: 100% |
| McClung (overall), 2001 [?] | age (yr): 74 (strate 1) and 83 (strate 2)<br>prevalent fractures (%): 39% and 44%<br>time since menopause (yr): 28 and 37 years |
| risedronate dose ranging (McClung), 1999 [?] | |

***Table 6.4:*** *Design and methodological quality of trials - biphosphonate - risedronate*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Risedronate versus placebo** | | | | |
| * VERT (Harris) 5 mg, 1999 [?] n=1633 | Parallel groups double-blind confirmatory trial at low risk of bias | 3 years inclusion period: dec 1993 - jan 1998 | North America 110 centres | vertebral fracture |
| * VERT europe (Reginster) 5mg, 2000 [?] n=814 | Parallel groups double-blind confirmatory trial at low risk of bias | 3 years | Europe, Australia 80 centres | vertebral fracture |
| BMD-MN (Fogelman), 2000 [?] n=543 | Parallel groups double-blind | 2 years | France, UK, the Netherlands, Belgium, Germany 13 centres | bone mineral density |
| Clemmesen, 1997 [?] (d) n=132 | Parallel groups double-blind exploratory trial | 3 years inclusion period: dec 1990 - jan 1992 | Denmark, Belgium 2 centres | none defined |
| McClung (overall), 2001 [?] n=9331 | Parallel groups double-blind | 3 years inclusion period: Nov 1993 - apr 1998 | Noth America, Europe, New Zealand, Australia 183 centres | hip fracture |
| risedronate dose ranging (McClung), 1999 [?] (f) n=648 | Parallel groups double-blind exploratory trial | 1.5 years | multicentre | BMD |

d) phase 2 f) dose ranging

## 6.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Risedronate versus placebo

A total of 4 of the 6 studies eligible for this comparison provided data on **vertebral fractures**. The analysis detected a statistically significant difference in favor of risedronate in vertebral fractures, with a RR of 0.64 (95% CI 0.53 to 0.77, p=0.0000). No heterogeneity was detected (p = 0.9452, $I^2$ = 0.00%).

A total of 3 of the 6 studies eligible for this comparison provided data on **hip fractures**. The analysis detected a statistically significant difference in favor of risedronate in hip fractures, with a RR of 0.68 (95% CI 0.50 to 0.92, p=0.0120). No heterogeneity was detected (p = 0.3136, $I^2$ = 0.14%).

A total of 3 of the 6 studies eligible for this comparison provided data on **major non vertebral fractures**. The analysis detected a statistically significant difference in favor of risedronate in major non vertebral fractures, with a RR of 0.76 (95% CI 0.65 to 0.89, p=0.0000). No heterogeneity was detected (p = 0.5765, $I^2$ = 0.00%).

All the 6 studies had extractable data about the number of participants with **non vertebral fractures**. The analysis detected a statistically significant difference in favor of risedronate in non vertebral fractures, with a RR of 0.77 (95% CI 0.66 to 0.89, p=0.0000). No heterogeneity was detected (p = 0.6398, $I^2$ = 0.00%).
A total of 2 of the 6 studies eligible for this comparison provided data on **1-year vertebral fracture**. The analysis detected a statistically significant difference in favor of risedronate in 1-year vertebral fracture, with a RR of 0.40 (95% CI 0.27 to 0.59, p=0.0000). No heterogeneity was detected (p = 0.7595, $I^2$ = 0.00%).
Only one of the 6 studies eligible for this comparison provided data on **morphometric vertebral fractures**. The analysis detected a statistically significant difference in favor of risedronate in morphometric vertebral fractures, with a RR of 0.66 (95% CI 0.49 to 0.90, p=0.0086).

***Table 6.5:*** *Results details - biphosphonate - risedronate*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***risedronate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.64 | [0.53;0.77] | 0.0000 | 0.9452 ($I^2$=0.00) | 4 | 2493 |
| hip fractures | RR=0.68 | [0.50;0.92] | 0.0120 | 0.3136 ($I^2$=0.14) | 3 | 12601 |
| major non vertebral fractures | RR=0.76 | [0.65;0.89] | 0.0000 | 0.5765 ($I^2$=0.00) | 3 | 11770 |
| non vertebral fractures | RR=0.77 | [0.66;0.89] | 0.0000 | 0.6398 ($I^2$=0.00) | 6 | 12847 |
| 1-year vertebral fracture | RR=0.40 | [0.27;0.59] | 0.0000 | 0.7595 ($I^2$=0.00) | 2 | 1996 |
| morphometric vertebral fractures | RR=0.66 | [0.49;0.90] | 0.0086 | 1.0000 ($I^2$=0.00) | 1 | 1633 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 6.1:*** *Forest's plot for vertebral fractures*

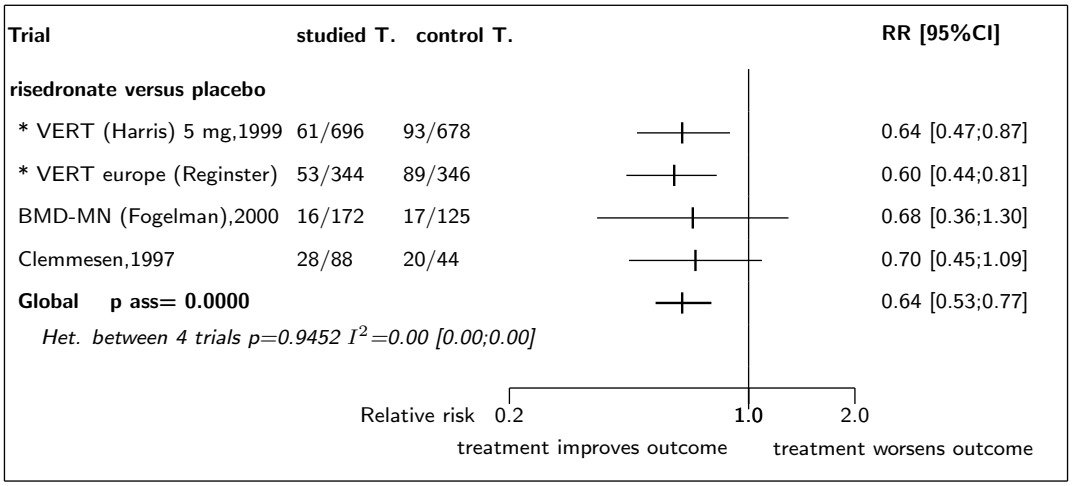


***Figure 6.2:*** *Forest's plot for hip fractures*

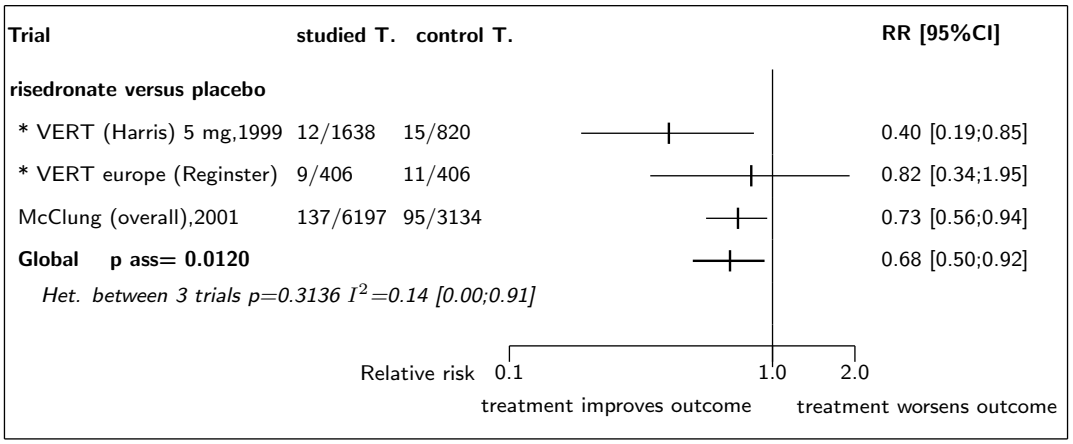



***Figure 6.3:*** *Forest's plot for major non vertebral fractures*

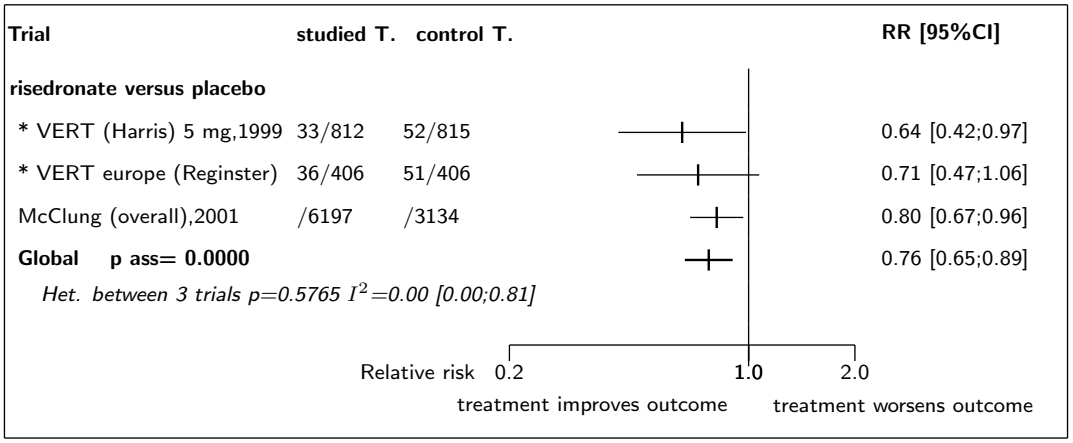


***Figure 6.4:*** *Forest's plot for non vertebral fractures*

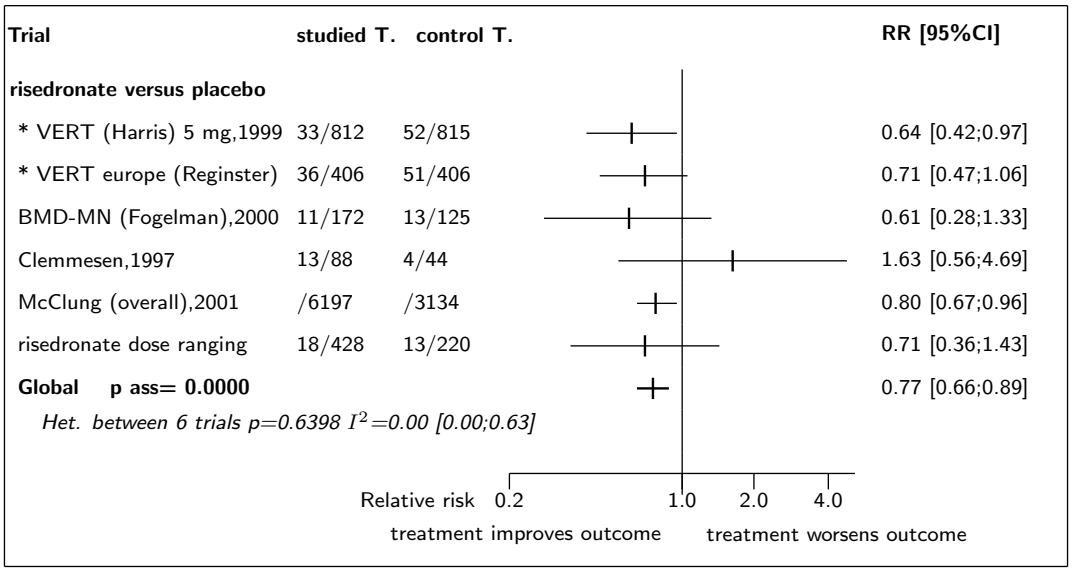



***Figure 6.5:*** *Forest's plot for 1-year vertebral fracture*

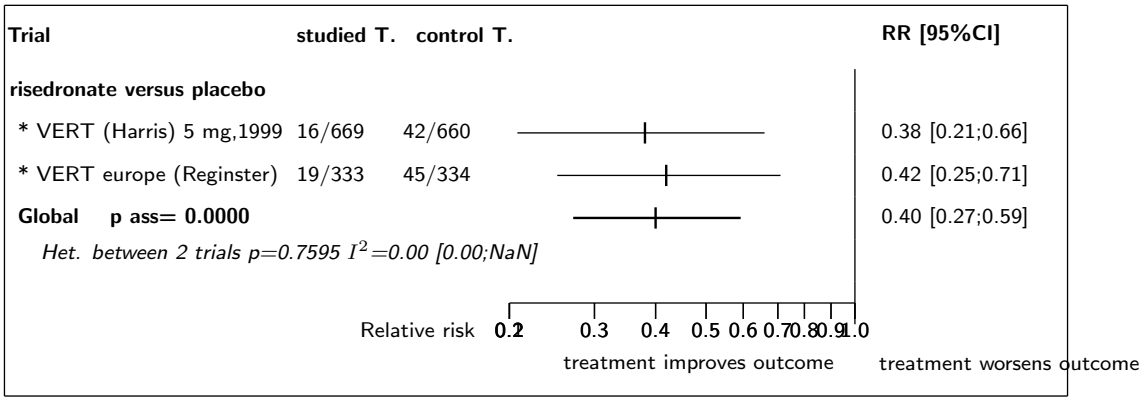
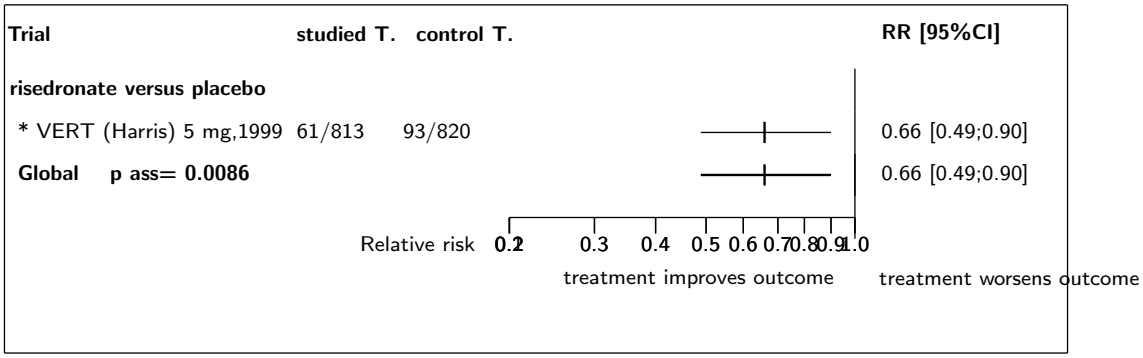



***Figure 6.6:*** *Forest's plot for morphometric vertebral fractures*



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## 6.3 Individual trial summaries

***Table 6.6:*** ** VERT (Harris) 5 mg, 1999 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=1633 (813 vs. 820)<br><br>**Follow-up duration:** 3 years<br><br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br><br>Confirmatory trial at low risk of bias<br><br>North America, 110 centres<br><br>**Inclusion period:** dec 1993 - jan 1998 | Ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline<br><br>**Inclusion criteria:** no older than 85 years; 5 years had elapsed since natural or surgical menopause; either 2 or more radiographically identified vertebral fractures (T4-L4, inclusive) or 1 vertebral fracture and low lumbar- spine (L1-L4) BMD (defined as <=0.83 g/cm2 [Hologic instrument] or <=0.94 g/cm2 [Lunar instrument]). These values represent a T score of 2 (2 SDs below the mean for young adults).<br><br>**Exclusion criteria:** conditions that might interfere with the evaluation of spinal bone loss; drugs known to affect bone metabolism (such as calcitonin, calcitriol or cholecalciferol supplements within 1 month prior to study entry; anabolic steroids, estrogen or estrogenrelated drugs, or progestins within 3 months; or bisphosphonates, fluoride, or subcutaneous estrogen implants within 6 months) | **Studied treatment:** oral treatment for 3 years with risedronate 5 mg/d<br><br>**Control treatment:** placebo<br><br>**Concomittant treat.:**calcium supplement equivalent to 1000 mg of elemental calcium daily, to be taken with the evening meal. Subjects with low serum 25-hydroxyvitamin D levels at baseline (,40 nmol/L) also received cholecalciferol supplementation (up to 500 IU/d)<br><br>**note:** initially 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d but the 2.5-mgarm was discontinued by protocol amendment (external evidence for less efficacy) | Vertebral fractures<br>RR=0.64 [0.47;0.87]<br>(new vertebral, table 2 (risedrone 2.5mg excluded))<br><br>Hip fractures<br>RR=0.40 [0.19;0.85]<br><br>Major non vertebral fractures<br>RR=0.64 [0.42;0.97]<br><br>Non vertebral fractures<br>RR=0.64 [0.42;0.97]<br><br>1-year vertebral fracture<br>RR=0.38 [0.21;0.66]<br>(for dose 5mg table 2)<br><br>Morphometric vertebral fractures<br>RR=0.66 [0.49;0.90]<br>(new fracture) |

**Reference**

Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD. 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;282:1344-52 [PMID=10527181]

***Table 6.7:*** ** VERT europe (Reginster) 5mg, 2000 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=814 (407 vs. 407)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Confirmatory trial at low risk of bias<br>Europe, Australia, 80 centres | Postmenopausal women with two or more prevalent vertebral fractures<br>**Inclusion criteria:** ambulatory women; up to 85 years old and at least 5 years postmenopausal; at least two radiographically confirmed vertebral (T4L4) fractures<br>**Exclusion criteria:** conditions thatmight interfere with evaluation of spinal osteoporosis; use of calcitonin, calcitriol or vitamin D supplementswithin 1 month, anabolic steroids, estrogen,estrogen-related drugs or progestogen within 3 months,or bisphosphonates, fluoride or subcutaneous estrogenimplant within 6 months. | **Studied treatment:** risedronate 5 mg/day for 3 years<br>**Control treatment:** placebo<br>**Concomittant treat.:**All patients received calcium 1000 mg/dayin a single dose with lunch or the evening meal and up to500 IU/day vitamin D if baseline 25-hydroxyvitamin Dlevels were below 40 nmol/l<br>**note:** 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d but 2.5 mggroup was discontinued after 2 years, | Vertebral fractures<br>RR=0.60 [0.44;0.81]<br>(table 2)<br>Hip fractures<br>RR=0.82 [0.34;1.95]<br>Major non vertebral fractures<br>RR=0.71 [0.47;1.06]<br>Non vertebral fractures<br>RR=0.71 [0.47;1.06]<br>(Osteoporosis-related)<br>1-year vertebral fracture<br>RR=0.42 [0.25;0.71]<br>(new vertebral fracture) |

**Reference**

Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91 [PMID=10663363]

***Table 6.8:*** *BMD-MN (Fogelman), 2000 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=543 (363 vs. 180)<br><br>**Follow-up duration:** 2 years<br><br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br><br>France, UK, the Netherlands, Belgium, Germany, 13 centres | Postmenopausal women with low bone mass<br><br>**Inclusion criteria:** women up to 80 yr of age; postmenopausal for at least 1 yr, based on the date of theirlast menstrual period; mean lumbar spine (L1L4) T-score of22 or less<br><br>**Exclusion criteria:** hyperparathyroidism,hyperthyroidism, or osteomalacia within a year beforethe study; a history of cancer; or abnormalities that would interfere withthe measurement of lumbar spine BMD by dual-energy x-ray absorptiometry; had taken (within612 months, depending on the medication) or were still taking treatmentknown to affect bone metabolism, including an injection of vitaminD >= 10,000IU | **Studied treatment:** Risedronate 2.5 mg/d or risedronate 5 mg/d<br><br>**Control treatment:** placebo<br><br>**Concomittant treat.:**dairy or other calcium-containing products at the same time as studymedication; elemental calcium (1g/day), as calcium carbonate, at a different time of day from the studydrug, preferably with food<br><br>**note:** 3 arms: placebo, Risedronate 2.5 mg/d, risedronate 5 mg/d. The 2.5-mg risedronate group was prematurely discontinuedby protocol amendment at 9 of the 13 centers, on the basis ofefficacy and safety assessments from other RCTs | Vertebral fractures<br>RR=0.68 [0.36;1.30]<br>(text p1899)<br><br>Non vertebral fractures<br>RR=0.61 [0.28;1.33]<br>(text p 1899) |

**Reference**

Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab 2000;85:1895-900 [PMID=10843171]

***Table 6.9:*** *Clemmesen, 1997 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=132 (88 vs. 44)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>Denmark, Belgium, 2 centres<br>**Inclusion period:** dec 1990 - jan 1992 | Patients with postmenopausal osteoporosis and at least one, but no more than four prevalent vertebral fractures at baseline<br>**Inclusion criteria:** otherwise healthypostmenopausal women, 5381 years of age and at least 1 year past the menopause, withestablished postmenopausal osteoporosis defined as atleast one, but no more than four vertebral fractures, andat least three intact lumbar vertebrae. | **Studied treatment:** 2.5 mg continuous risedronate or 2.5 mg cyclic risedronate for 2 years<br>cyclic risedronate = 2.5 mg daily risedronate for 2 weeksfollowed by 10 weeks on placebo<br>**Control treatment:** placebo<br>**Concomittant treat.:**calcium supplement 1 g daily<br>**note:** 3 arms: placebo, 2.5 mg continuous risedronate, 2.5 mg cyclic risedronate | Vertebral fractures<br>RR=0.70 [0.45;1.09]<br>(new vertebral fractures table 3)<br>Non vertebral fractures<br>RR=1.63 [0.56;4.69]<br>(table 3) |

**Reference**

Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int 1997;7:488-95 [PMID=9425508]

***Table 6.10:*** *McClung (overall), 2001 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=9331 (6197 vs. 3134)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Noth America, Europe, New Zealand, Australia, 183 centres<br>**Inclusion period:** Nov 1993 - apr 1998 | Women 70 to 79 years old with osteoporosis and women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck<br>**Inclusion criteria:** women 70 to 79 years old who had osteoporosis (indicated by a T score for bone mineral density at the femoral neck that was more than 4 SD below the mean peak value in young adults or lower than -3 plus a nonskeletal risk factor for hip fracture, such as poor gait or a propensity to fall) and women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck (T score, lower than -4 or lower than -3 plus a hip-axis length of 11.1 cm or greater) | **Studied treatment:** oral risedronate (2.5 or 5.0 mg daily)<br>**Control treatment:** placebo<br>**note:** 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d | Hip fractures<br>RR=0.73 [0.56;0.94]<br>(table 2 radiographically confirmed hip fractures) |

**Reference**

McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40 [PMID=11172164]

***Table 6.11:*** *risedronate dose ranging (McClung), 1999 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=648 (428 vs. 220)<br>**Follow-up duration:** 1.5 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>multicentre | Menopausal women with low BMD (T-score <-2) | **Studied treatment:** Risedronate 2.5 mg/d or risedronate 5 mg/d for up to 18 months<br>**Control treatment:** placebo<br>**Concomittant treat.:**supplemental calcium 1g daily<br>**note:** 3 arms: placebo, risedronate 2.5 mg/d, risedronate 5 mg/d | Non vertebral fractures<br>RR=0.71 [0.36;1.43] |

**Reference**

McClung M, Bensen W, Bolognese M, Bonnick SL, Esinger MP,Harris ST, Heath H, Lang R, Miller PD, Pavio EP, Silverman, SL. Risedronate increases bone mineral density at the hip, spine,and radius in postmenopausal women with low bone mass. OsteoporosInt 1998;8:111 (Abstract)

# 7 Global meta-analysis: all biphosphonate

## 7.1 Global meta-analysis: all biphosphonate versus control

***Table 7.1:*** *All biphosphonateversus control*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| vertebral fractures | RR=0.15 | 0.01;2.95 | 0.2137 | 1.0000 (0.00) | 1 | 71 |

legend B

## 7.2 Global meta-analysis: all biphosphonate versus placebo

***Table 7.2:*** *All biphosphonateversus placebo*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| vertebral fractures | RR=0.59 | 0.51;0.68 | 0.0000 | 0.9872 (0.00) | 10 | 10003 |
| clinical vertebral fractures | RR=0.45 | 0.28;0.74 | 0.0000 | 1.0000 (0.00) | 1 | 2027 |
| hip fractures | RR=0.68 | 0.55;0.83 | 0.0000 | 0.8814 (0.00) | 10 | 24100 |
| major non vertebral fractures | RR=0.82 | 0.66;1.02 | 0.0753 | 0.1158 (0.49) | 4 | 13722 |
| non vertebral fractures | RR=0.82 | 0.75;0.90 | 0.0000 | 0.4019 (0.04) | 14 | 24705 |
| 1-year vertebral fracture | RR=0.44 | 0.31;0.62 | 0.0000 | 0.7378 (0.00) | 4 | 4009 |
| 1-year non vertebral fracture | RR=0.52 | 0.30;0.89 | 0.0181 | 1.0000 (0.00) | 1 | 1908 |
| morphometric vertebral fractures | RR=0.56 | 0.48;0.65 | 0.0000 | 0.7923 (0.00) | 5 | 10627 |

legend B

# 8 Ongoing studies of biphosphonate

No ongoing trial was identified.

# 9 Excluded studies for biphosphonate

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

***Table 9.1:*** *Excluded studies of biphosphonate*

| **Study** | **Exclusion reason** |
|---|---|
| Ascott Evans (2003) [**?**] | insufficient follow-up |
| Bonnick (0) [**?**] | |
| Durson (2001) [**?**] | insufficient follow-up duration |
| Greenspan (2002) [**?**] | follow-up duration insufficient (12 weeks) |
| Hosking 5mg (1998) [**?**] | prevention trial |
| Lyritis (1997) [**?**] | not randomized (described as cohort study) |
| Pacifici (1998) [**?**] | special regimen of etidronate, not comparable to the treatment applied in the others trials |
| * HORIZON (Black) (2007) [**?**] | |

# Part II

# Strontium ranelate

# 10 Overview of strontium ranelate

## 10.1 Included trials

A total of 4 randomized comparisons which enrolled 7078 patients were identified. In all, 4 randomized comparisons concerned strontium ranelate.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for strontium ranelate.

The average study size was 1769 patients (range 160 to 5091). The first study was published in 2002, and the last study was published in 2004.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

## 10.2 Summary of meta-analysis results

The meta-analysis of the available trials about strontium ranelate provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

### 10.2.1 Strontium ranelate

**Strontium ranelate** was superior to **placebo** in terms of vertebral fractures (RR=0.60, 95% CI 0.52 to 0.69, p=0.0000, 2 trials), clinical vertebral fractures (RR=0.62, 95% CI 0.47 to 0.82, p=0.0000, 1 trial), major non vertebral fractures (RR=0.86, 95% CI 0.73 to 1.00, p=0.0479, 2 trials), non vertebral fractures (RR=0.87, 95% CI 0.76 to 1.00, p=0.0449, 2 trials), 1-year vertebral fracture (RR=0.53, 95% CI 0.42 to 0.68, p=0.0000, 2 trials)and morphometric vertebral fractures (RR=0.62, 95% CI 0.54 to 0.71, p=0.0000, 3 trials). However, no significant difference was found on hip fractures (RR=0.85, 95% CI 0.61 to 1.19, p=0.3404, 1 trial).

***Table 10.1:*** *Main study characteristics - strontium ranelate*

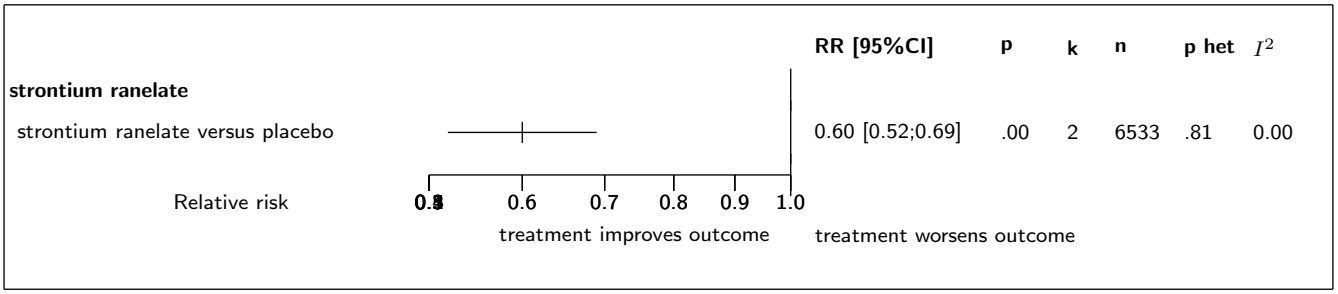
| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| **Strontium ranelate** | | | |
| ***Strontium ranelate versus placebo*** | | | |
| PREVOS (Reginster), 2002 [**?**]<br>n = 120 vs. 40 | early postmenopausal women | strontium ranelate (SR) 125 mg/day, 500 mg/day or 1 g/day for 2 years<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: lumbar bone mineral density<br>2 centres,France, Belgium |
| SOTI (Meunier), 2004 [**?**]<br>n = 828 vs. 821 | postmenopausal women with osteoporosis and at least one vertebral fracture | oral strontium ranelate 2 g daily for 3 years<br>**versus**<br>placebo<br>treatment duration: 3 years | double-blind<br>parallel groups<br>Primary endpoint: vertebral fractures<br>72 centres,Europe, Australia |
| STRATOS (Meunier) 2g/d, 2002 [**?**]<br>n = 87 vs. 91 | osteoporotic women with at least one previous vertebral fracture and a lumbar T-score <-2.4 | strontium 2g for 2 years<br>**versus**<br>placebo<br>treatment duration: 2 years | double-blind<br>parallel groups<br>Primary endpoint: lumbar BMD annual slope<br>31 centres,Europe (9 countries) |
| TROPOS (Reginster), 2004 [**?**]<br>n = 2554 vs. 2537 | postmenopausal women with osteoporosis | strontium ranelate (2 g/d)<br>**versus**<br>placebo | double-blind<br>parallel groups<br>Primary endpoint: nonvertebral fractures<br>75 centres,Europe, Australia |

***Table 10.2:*** *Summary of all results for strontium ranelate*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***strontium ranelate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.60 | 0.52;0.69 | 0.0000 | 0.8128 (0.00) | 2 | 6533 |
| clinical vertebral fractures | RR=0.62 | 0.47;0.82 | 0.0000 | 1.0000 (1.00) | 1 | 1442 |
| hip fractures | RR=0.85 | 0.61;1.19 | 0.3404 | 1.0000 (1.00) | 1 | 5091 |
| major non vertebral fractures | RR=0.86 | 0.73;1.00 | 0.0479 | 0.4088 (0.00) | 2 | 6533 |
| non vertebral fractures | RR=0.87 | 0.76;1.00 | 0.0449 | 0.5244 (0.00) | 2 | 6533 |
| 1-year vertebral fracture | RR=0.53 | 0.42;0.68 | 0.0000 | 0.7629 (0.00) | 2 | 6533 |
| morphometric vertebral fractures | RR=0.62 | 0.54;0.71 | 0.0000 | 0.4037 (0.00) | 3 | 6711 |

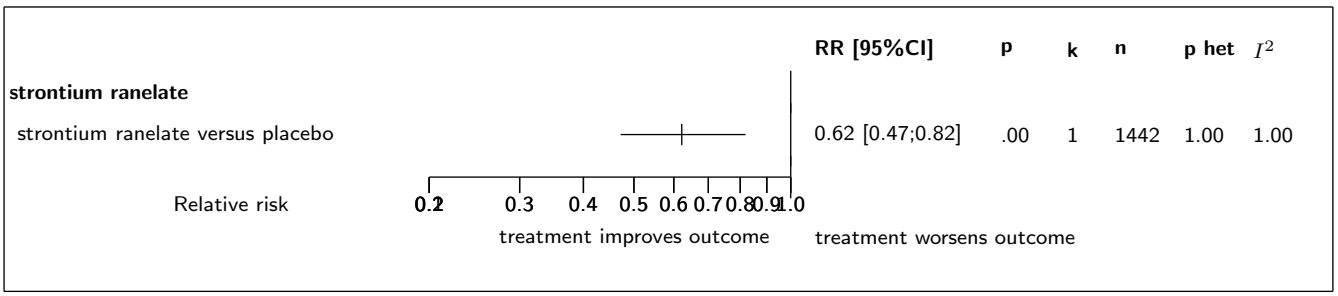
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

***Figure 10.1:*** *Forest's plot for vertebral fractures*



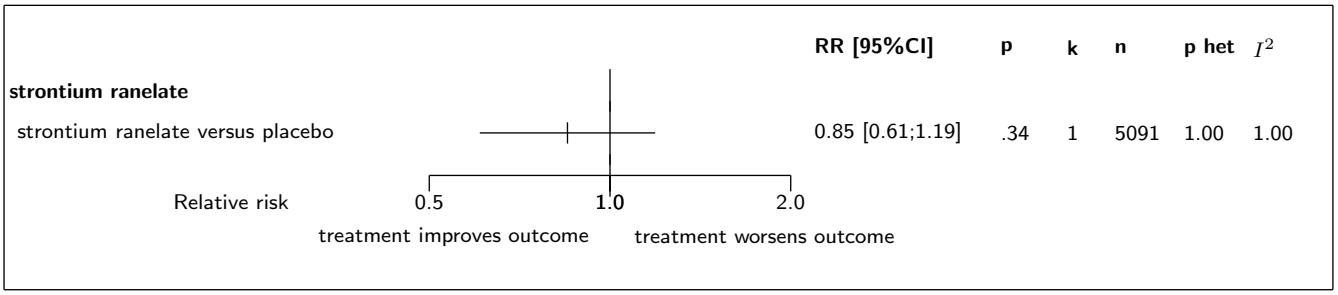

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 10.2:*** *Forest's plot for clinical vertebral fractures*



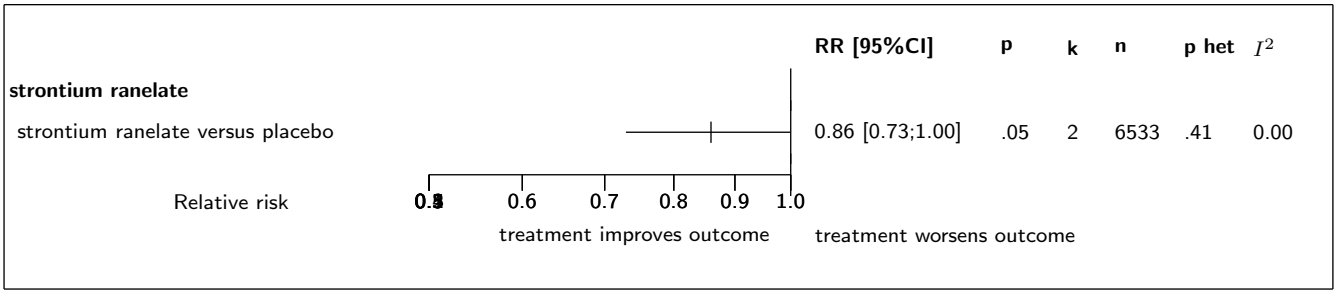

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 10.3:*** *Forest's plot for hip fractures*



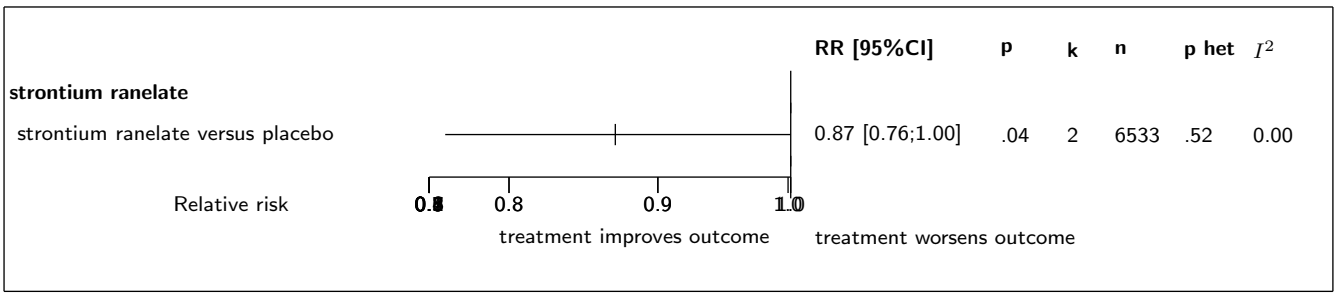

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 10.4:*** *Forest's plot for major non vertebral fractures*



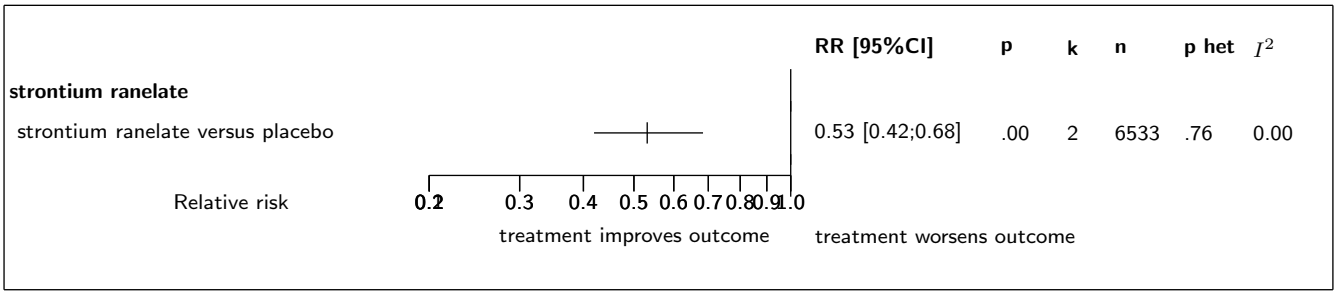

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 10.5:*** *Forest's plot for non vertebral fractures*



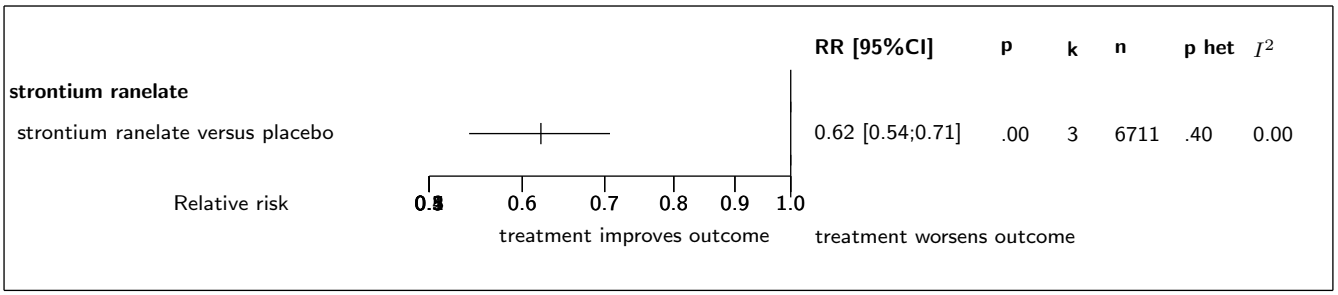

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 10.6:*** *Forest's plot for 1-year vertebral fracture*




Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 10.7:*** *Forest's plot for morphometric vertebral fractures*




Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

# 11 Details

## 11.1 Available trials

A total of 4 RCTs which randomized 7078 patients were identified: all compared strontium ranelate with placebo.
The average study size was 1769 patients (range 160 to 5091). The first study was published in 2002, and the last study was published in 2004.
All trials were double blind in design. All included studies were reported in English language.
We did not found any unpublished trial.
Non vertebral fractures data was reported in 1 trials; and 1 trials reported data on major non vertebral fractures.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of strontium ranelate.

***Table 11.1:*** *Treatment description - strontium ranelate - strontium ranelate*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Strontium ranelate versus placebo** | | |
| PREVOS (Reginster) (2002) [**?**] [a] | strontium ranelate (SR) 125 mg/day, 500 mg/day or 1 g/day for 2 years<br><br>**Concomittant treatment:** calcium 500 mg daily | placebo |
| SOTI (Meunier) (2004) [**?**] | oral strontium ranelate 2 g daily for 3 years<br><br>**Concomittant treatment:** daily calcium supplements at lunchtime (up to 1000 mg of elemental calcium, depending on their dietary calcium intake), to maintain a daily calcium intake above 1500 mg, and vitamin D (400 to 800 IU, depending on the base-line serum concentration of 25-hydroxyvitamin D) | placebo |
| STRATOS (Meunier) 2g/d (2002) [**?**] [c] | strontium 2g for 2 years | placebo |
| TROPOS (Reginster) (2004) [**?**] | Strontium ranelate (2 g/d) | placebo |

a) 4 arms: placebo, strontium ranelate, 125 mg/day, 500 mg/day or 1 g/day for 2 years c) 4 arms placebo, strontium 0.5 g, 1 g, or 2 g

***Table 11.2:*** *Descriptions of participants - strontium ranelate - strontium ranelate*

| Trial | Patients |
|---|---|
| **Strontium ranelate versus placebo** | |

continued...

| Trial | Patients | |
|---|---|---|
| PREVOS (Reginster) (2002) [?] | Early postmenopausal women | |
| | **Inclusion criteria:** naturally postmenopausal Caucasian women aged atleast 45 years; postmenopausal for 6 months to 5 years; bodymass index less than 30 kg/m2 and no knownosteoporosis and/or known vertebral or femoral fragilityfractures | **Exclusion criteria:** menopause before the age of 45 years, bilateral oophorectomy, progressive bone diseases (e.g., Pagets disease, bone cancer), chronic conditions affecting bone metabolism (e.g., renal or hepatic failure), treatment during the previous 3 months with agents affecting bone metabolism (e.g., ERT, calcium 4500 mg/day, vitamin D, phosphorus, calcitonin, corticosteroids, thiazide diuretics), previous treatment with fluoride for 48 days or bisphosphonates for 415 days (no treatment with fluoride or bisphosphonates was permitted during the previous 6 months) |
| SOTI (Meunier) (2004) [?] | Postmenopausal women with osteoporosis and at least one vertebral fracture | |
| | **Inclusion criteria:** at least 50 years old; postmenopausal for at least five years; at least one fracture confirmed by spinal radiography (after minimal trauma); lumbar-spine bone mineral density of 0.840 g per square centimeter or less (measured with Hologic instruments) | **Exclusion criteria:** severe diseases or conditions that could interfere with bone metabolism; antiosteoporotic treatments (fluoride salts and bisphosphonates taken for more than 14 days within the previous 12 months, or estrogen, calcitonin, or calcitriol taken for more than 1 month in the previous 6 months) |
| STRATOS (Meunier) 2g/d (2002) [?] | Osteoporotic women with at least one previous vertebral fracture and a lumbar T-score <-2.4 | |
| TROPOS (Reginster) (2004) [?] | Postmenopausal women with osteoporosis | |
| | **Inclusion criteria:** femoral neck bonemineral density (BMD) 0.600 g/cm2 or less (measured with Hologicinstruments), corresponding to a T-score less than 2.5 according to thecentralized normative data (D. O. Slosman); 74 yr or older,or aged between 70 and 74 yr but with one additional fracture risk factor(i.e. history of osteoporotic fracture after menopause, residence in aretirement home, frequent falls, or a maternal history of osteoporoticfractures of the hip, spine, or wrist) | **Exclusion criteria:** diseases interfering with bone metabolism oruse of anti-osteoporotic treatments (bisphosphonates taken for morethan 14 d within the previous year; estrogen, calcitonin, fluoride salts,calcitriol, or 1–vitamin D taken for more than 1 month during theprevious 6 months) |

***Table 11.3:*** *Main patients characteristics - strontium ranelate - strontium ranelate*

| Trial | Characteristics |
|---|---|
| **Strontium ranelate versus placebo** | |
| PREVOS (Reginster), 2002 [**?**] | age (yr): 54 y<br>time since menopause (yr): 37 y<br>t-score (lumbar): -1.425<br>BMD: 0.932 (lumbar L2-L4) |
| SOTI (Meunier), 2004 [**?**] | age (yr): 69.3 y<br>time since menopause (yr): 21.85 y<br>t-score (lumbar): -3.55<br>BMD: 0.73 g/cm2 (lumbar spine)<br>low BMD as inclusion criteria: yes<br>low BMD as criteria: yes<br>prevalent fracture as criteria: 100%<br>prevalente fracture at baseline: 100% |
| STRATOS (Meunier) 2g/d, 2002 [**?**] | age (yr): 66.16 yr<br>BMD inclusion criteria: lumbar T score <-2.4<br>prevalent fractures (%): 100%<br>time since menopause (yr): 18.32 y<br>t-score (lumbar): -3.92<br>BMD: 0.69 g/cm2 (lumbar)<br>low BMD as inclusion criteria: <-2.4<br>low BMD as criteria: yes<br>prevalent fracture as criteria: yes<br>inclusion without BMD: no<br>prevalente fracture at baseline: 100% |
| TROPOS (Reginster), 2004 [**?**] | age (yr): 76.7 y<br>prevalent fractures (%): 55.3%<br>time since menopause (yr): 28.4 y<br>t-score (lumbar): -2.83 |

***Table 11.4:*** *Design and methodological quality of trials - strontium ranelate - strontium ranelate*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Strontium ranelate versus placebo** | | | | |
| PREVOS (Reginster), 2002 [**?**] [(a)] n=160 | Parallel groups double-blind exploratory trial | 2 years | France, Belgium 2 centres | lumbar bone mineral density |
| SOTI (Meunier), 2004 [**?**] [(b)] n=1649 | Parallel groups double-blind confirmatory trial at low risk of bias | 3 years inclusion period: Nov 1996 - Jul 1998 | Europe, Australia 72 centres | vertebral fractures |
| STRATOS (Meunier) 2g/d, 2002 [**?**] [(c)] n=178 | Parallel groups double-blind exploratory trial | 2 years inclusion period: NA | Europe (9 countries) 31 centres | lumbar BMD annual slope |
| TROPOS (Reginster), 2004 [**?**] n=5091 | Parallel groups double-blind confirmatory trial at low risk of bias | 3 years | Europe, Australia 75 centres | nonvertebral fractures |

continued...

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|

a) phase 2 b) 198 patients excluded after randomization for no radiograph after baseline c) phase 2, dose ranging

## 11.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Strontium ranelate versus placebo

A total of 2 of the 4 studies eligible for this comparison provided data on **vertebral fractures**. The analysis detected a statistically significant difference in favor of strontium ranelate in vertebral fractures, with a RR of 0.60 (95% CI 0.52 to 0.69, p=0.0000). No heterogeneity was detected (p = 0.8128, $I^2$ = 0.00%).
Only one of the 4 studies eligible for this comparison provided data on **clinical vertebral fractures**. The analysis detected a statistically significant difference in favor of strontium ranelate in clinical vertebral fractures, with a RR of 0.62 (95% CI 0.47 to 0.82, p=0.0000).
Only one of the 4 studies eligible for this comparison provided data on **hip fractures**. No statistically significant difference between the groups was found in hip fractures, with a RR of 0.85 (95% CI 0.61 to 1.19, p=0.3404).
A total of 2 of the 4 studies eligible for this comparison provided data on **major non vertebral fractures**. The analysis detected a statistically significant difference in favor of strontium ranelate in major non vertebral fractures, with a RR of 0.86 (95% CI 0.73 to 1.00, p=0.0479). No heterogeneity was detected (p = 0.4088, $I^2$ = 0.00%).
A total of 2 of the 4 studies eligible for this comparison provided data on **non vertebral fractures**. The analysis detected a statistically significant difference in favor of strontium ranelate in non vertebral fractures, with a RR of 0.87 (95% CI 0.76 to 1.00, p=0.0449). No heterogeneity was detected (p = 0.5244, $I^2$ = 0.00%).
A total of 2 of the 4 studies eligible for this comparison provided data on **1-year vertebral fracture**. The analysis detected a statistically significant difference in favor of strontium ranelate in 1-year vertebral fracture, with a RR of 0.53 (95% CI 0.42 to 0.68, p=0.0000). No heterogeneity was detected (p = 0.7629, $I^2$ = 0.00%).
A total of 3 of the 4 studies eligible for this comparison provided data on **morphometric vertebral fractures**. The analysis detected a statistically significant difference in favor of strontium ranelate in morphometric vertebral fractures, with a RR of 0.62 (95% CI 0.54 to 0.71, p=0.0000). No heterogeneity was detected (p = 0.4037, $I^2$ = 0.00%).

***Table 11.5:*** *Results details - strontium ranelate - strontium ranelate*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***strontium ranelate versus placebo*** | | | | | | |
| vertebral fractures | RR=0.60 | [0.52;0.69] | 0.0000 | 0.8128 ($I^2$=0.00) | 2 | 6533 |
| clinical vertebral fractures | RR=0.62 | [0.47;0.82] | 0.0000 | 1.0000 ($I^2$=1.00) | 1 | 1442 |
| hip fractures | RR=0.85 | [0.61;1.19] | 0.3404 | 1.0000 ($I^2$=1.00) | 1 | 5091 |
| major non vertebral fractures | RR=0.86 | [0.73;1.00] | 0.0479 | 0.4088 ($I^2$=0.00) | 2 | 6533 |
| non vertebral fractures | RR=0.87 | [0.76;1.00] | 0.0449 | 0.5244 ($I^2$=0.00) | 2 | 6533 |
| 1-year vertebral fracture | RR=0.53 | [0.42;0.68] | 0.0000 | 0.7629 ($I^2$=0.00) | 2 | 6533 |
| morphometric vertebral fractures | RR=0.62 | [0.54;0.71] | 0.0000 | 0.4037 ($I^2$=0.00) | 3 | 6711 |

continued...

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 11.1:*** *Forest's plot for vertebral fractures*

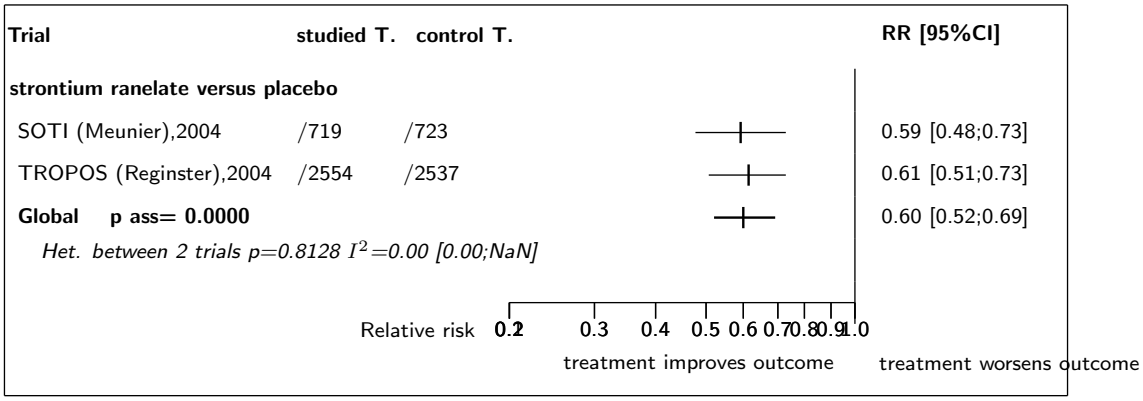



***Figure 11.2:*** *Forest's plot for clinical vertebral fractures*

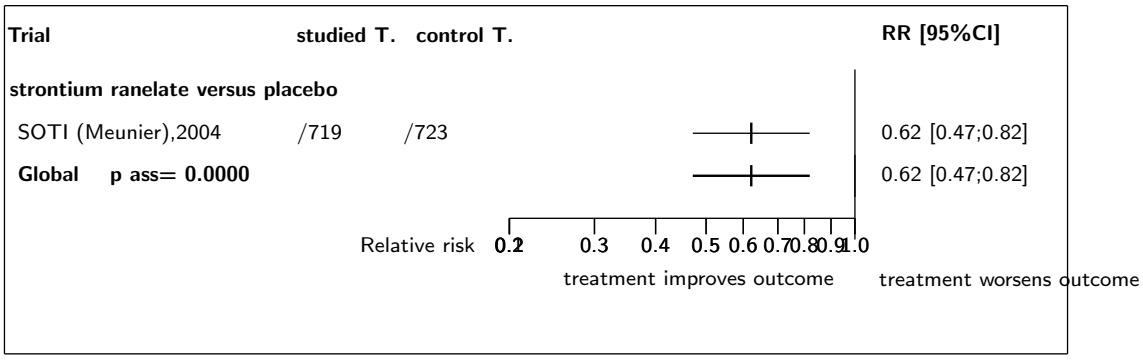



***Figure 11.3:*** *Forest's plot for hip fractures*

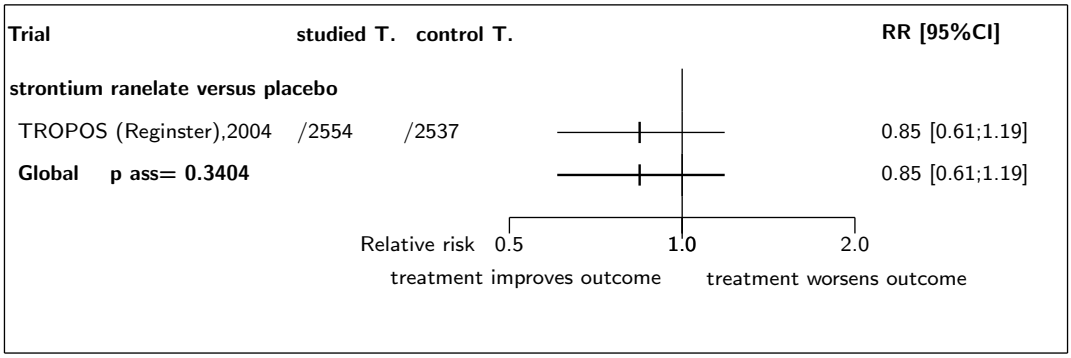


***Figure 11.4:*** *Forest's plot for major non vertebral fractures*

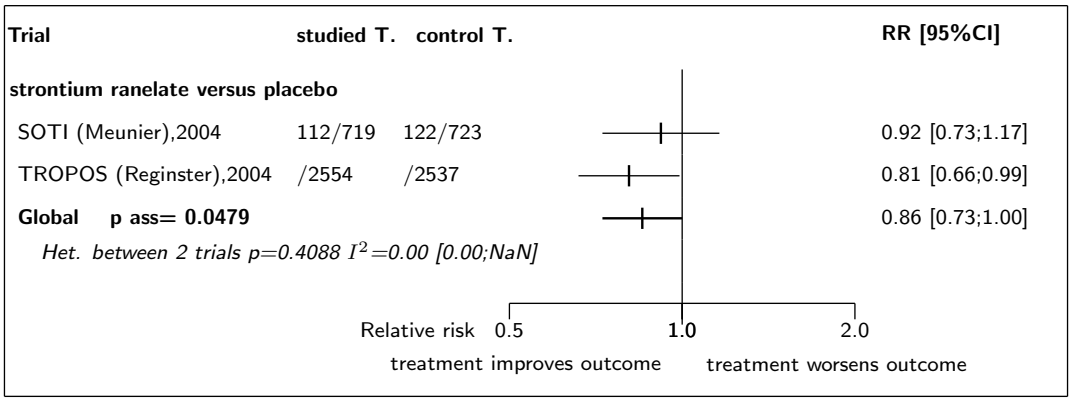



***Figure 11.5:*** *Forest's plot for non vertebral fractures*

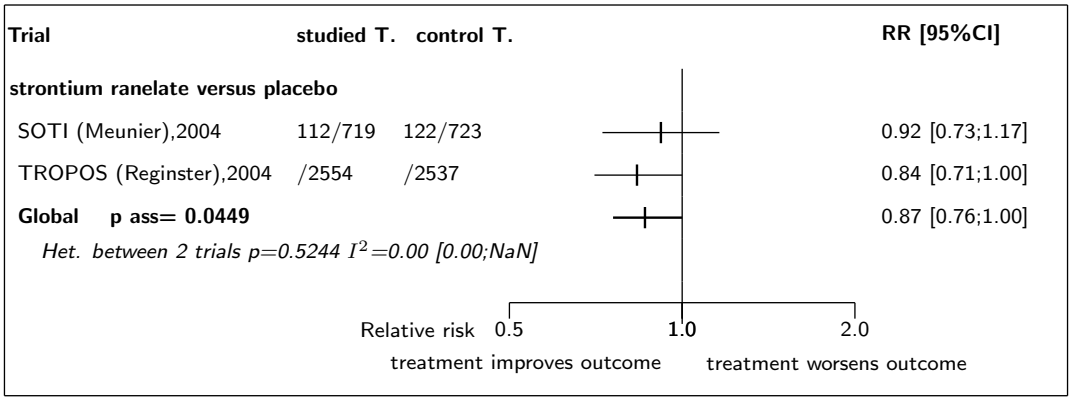



***Figure 11.6:*** *Forest's plot for 1-year vertebral fracture*

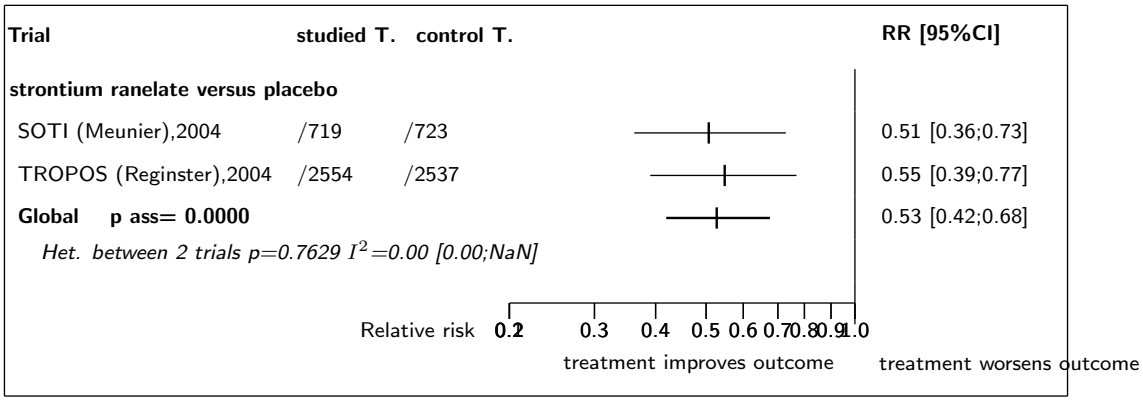
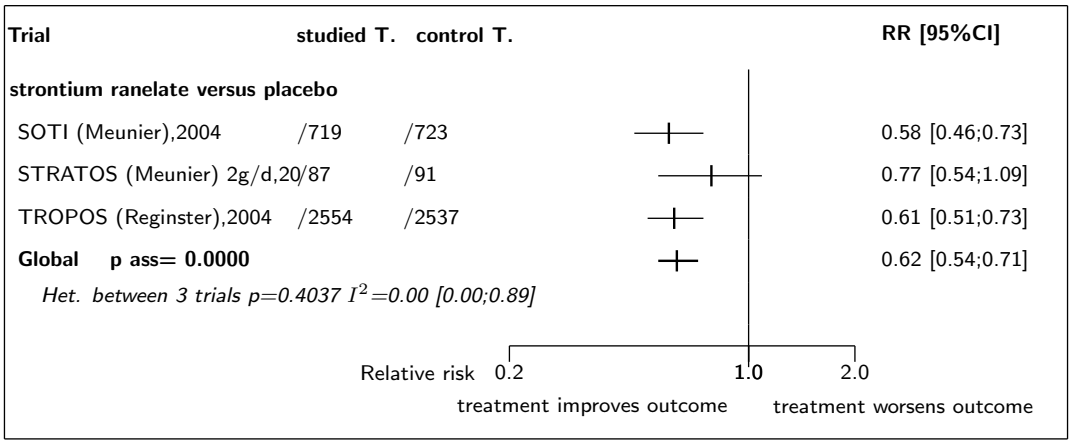


***Figure 11.7:*** *Forest's plot for morphometric vertebral fractures*




# References

[1] Reginster JY, Deroisy R, Dougados M, Jupsin I, Colette J, Roux C. Prevention of early postmenopausal bone loss by strontium ranelate: the randomized, two-year, double-masked, dose-ranging, placebo-controlled PREVOS trial. Osteoporos Int 2002;13:925-31. [PMID=12459934]

[2] Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, Cannata J, Balogh A, Lemmel EM, Pors-Nielsen S, Rizzoli R, Genant HK, Reginster JY. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350:459-68. [PMID=14749454]

[3] Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, Lorenc R, Pors-Nielsen S, De Vernejoul MC, Roces A, Reginster JY. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis–a 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002;87:2060-6. [PMID=11994341]

[4] Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, Devogelaer JP, Curiel MD, Sawicki A, Goemaere S, Sorensen OH, Felsenberg D, Meunier PJ. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90:2816-22. [PMID=15728210]

## 11.3 Individual trial summaries

***Table 11.6:*** *PREVOS (Reginster), 2002 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=160 (120 vs. 40)<br>**Follow-up duration:** 2 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>France, Belgium, 2 centres | Early postmenopausal women<br>**Inclusion criteria:** Naturally postmenopausal Caucasian women aged atleast 45 years; postmenopausal for 6 months to 5 years; bodymass index less than 30 kg/m2 and no knownosteoporosis and/or known vertebral or femoral fragilityfractures<br>**Exclusion criteria:** menopause before the age of 45 years, bilateral oophorectomy, progressive bone diseases (e.g., Pagets disease, bone cancer), chronic conditions affecting bone metabolism (e.g., renal or hepatic failure), treatment during the previous 3 months with agents affecting bone metabolism (e.g., ERT, calcium 4500 mg/day, vitamin D, phosphorus, calcitonin, corticosteroids, thiazide diuretics), previous treatment with fluoride for 48 days or bisphosphonates for 415 days (no treatment with fluoride or bisphosphonates was permitted during the previous 6 months) | **Studied treatment:** strontium ranelate (SR) 125 mg/day, 500 mg/day or 1 g/day for 2 years<br>**Control treatment:** placebo<br>**Concomittant treat.:**calcium 500 mg daily<br>**note:** 4 arms: placebo, strontium ranelate, 125 mg/day, 500 mg/day or 1 g/day for 2 years | |

**Reference**

Reginster JY, Deroisy R, Dougados M, Jupsin I, Colette J, Roux C. Prevention of early postmenopausal bone loss by strontium ranelate: the randomized, two-year, double-masked, dose-ranging, placebo-controlled PREVOS trial. Osteoporos Int 2002;13:925-31 [PMID=12459934]

***Table 11.7:*** *SOTI (Meunier), 2004 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=1649 (828 vs. 821)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Confirmatory trial at low risk of bias<br>Europe, Australia, 72 centres<br>**Inclusion period:** Nov 1996 - Jul 1998 | Postmenopausal women with osteoporosis and at least one vertebral fracture<br>**Inclusion criteria:** at least 50 years old; postmenopausal for at least five years; at least one fracture confirmed by spinal radiography (after minimal trauma); lumbar-spine bone mineral density of 0.840 g per square centimeter or less (measured with Hologic instruments)<br>**Exclusion criteria:** severe diseases or conditions that could interfere with bone metabolism; antiosteoporotic treatments (fluoride salts and bisphosphonates taken for more than 14 days within the previous 12 months, or estrogen, calcitonin, or calcitriol taken for more than 1 month in the previous 6 months) | **Studied treatment:** oral strontium ranelate 2 g daily for 3 years<br>**Control treatment:** placebo<br>**Concomittant treat.:**daily calcium supplements at lunchtime (up to 1000 mg of elemental calcium, depending on their dietary calcium intake), to maintain a daily calcium intake above 1500 mg, and vitamin D (400 to 800 IU, depending on the base-line serum concentration of 25-hydroxyvitamin D) | Major non vertebral fractures<br>RR=0.92 [0.73;1.17]<br>Non vertebral fractures<br>RR=0.92 [0.73;1.17] |

**Reference**

Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, Cannata J, Balogh A, Lemmel EM, Pors-Nielsen S, Rizzoli R, Genant HK, Reginster JY. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350:459-68 [PMID=14749454]

***Table 11.8:*** *STRATOS (Meunier) 2g/d, 2002 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=178 (87 vs. 91)<br>**Follow-up duration:** 2 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Exploratory trial<br>Europe (9 countries), 31 centres<br>**Inclusion period:** NA | Osteoporotic women with at least one previous vertebral fracture and a lumbar T-score <-2.4 | **Studied treatment:** strontium 2g for 2 years<br>**Control treatment:** placebo<br>**note:** 4 arms placebo, strontium 0.5 g, 1 g, or 2 g | |

**Reference**

Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, Lorenc R, Pors-Nielsen S, De Vernejoul MC, Roces A, Reginster JY. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis–a 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002;87:2060-6 [PMID=11994341]

***Table 11.9:*** *TROPOS (Reginster), 2004 - Trial synopsis*

| Trial details | Patients | Treatments | Outcomes |
|---|---|---|---|
| n=5091 (2554 vs. 2537)<br>**Follow-up duration:** 3 years<br>**Study design:** Randomized controlled trial<br>Parallel groups<br>Double-blind<br>Confirmatory trial at low risk of bias<br>Europe, Australia, 75 centres | Postmenopausal women with osteoporosis<br>**Inclusion criteria:** femoral neck bonemineral density (BMD) 0.600 g/cm2 or less (measured with Hologicinstruments), corresponding to a T-score less than 2.5 according to thecentralized normative data (D. O. Slosman); 74 yr or older,or aged between 70 and 74 yr but with one additional fracture risk factor(i.e. history of osteoporotic fracture after menopause, residence in aretirement home, frequent falls, or a maternal history of osteoporoticfractures of the hip, spine, or wrist)<br>**Exclusion criteria:** diseases interfering with bone metabolism oruse of anti-osteoporotic treatments (bisphosphonates taken for morethan 14 d within the previous year; estrogen, calcitonin, fluoride salts,calcitriol, or 1–vitamin D taken for more than 1 month during theprevious 6 months) | **Studied treatment:** Strontium ranelate (2 g/d)<br>**Control treatment:** placebo | |

**Reference**

Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, Devogelaer JP, Curiel MD, Sawicki A, Goemaere S, Sorensen OH, Felsenberg D, Meunier PJ. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90:2816-22 [PMID=15728210]

# 12 Global meta-analysis: all strontium ranelate

## 12.1 Global meta-analysis: all strontium ranelate versus placebo

***Table 12.1:*** *All strontium ranelateversus placebo*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| vertebral fractures | RR=0.60 | 0.52;0.69 | 0.0000 | 0.8128 (0.00) | 2 | 6533 |
| clinical vertebral fractures | RR=0.62 | 0.47;0.82 | 0.0000 | 1.0000 (1.00) | 1 | 1442 |
| hip fractures | RR=0.85 | 0.61;1.19 | 0.3404 | 1.0000 (1.00) | 1 | 5091 |
| major non vertebral fractures | RR=0.86 | 0.73;1.00 | 0.0479 | 0.4088 (0.00) | 2 | 6533 |
| non vertebral fractures | RR=0.87 | 0.76;1.00 | 0.0449 | 0.5244 (0.00) | 2 | 6533 |
| 1-year vertebral fracture | RR=0.53 | 0.42;0.68 | 0.0000 | 0.7629 (0.00) | 2 | 6533 |
| morphometric vertebral fractures | RR=0.62 | 0.54;0.71 | 0.0000 | 0.4037 (0.00) | 3 | 6711 |

legend B

# 13 Ongoing studies of strontium ranelate

No ongoing trial was identified.

# 14 Excluded studies for strontium ranelate

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

***Table 14.1:*** *Excluded studies of strontium ranelate*

| Study | Exclusion reason |
|---|---|
| Hwang (2008) [**?**] | no fracture data |
| Liu (2009) [**?**] | no fracture data |