Extract from

DSU report by Dr Matt Stevenson, Dr Myfanwy Lloyd Jones, Ms Sarah Davis and Ms Catherine Beverly; ScHARR, 3rd March 2005

3 CLINICAL EFFECTIVENESS

Literature searches

A review of the efficacy of interventions for the treatment and prevention of osteoporosis carried out by the authors has been previously reported. [15] The electronic literature searches undertaken in 2002 were updated in November 2004.

Inclusion criteria

The inclusion criteria for population, outcome measures and study design were the same as those used in the original review. However, only the following interventions were included:

- bisphosphonates
  - alendronate
  - etidronate
  - risedronate
- SERMs
  - raloxifene.

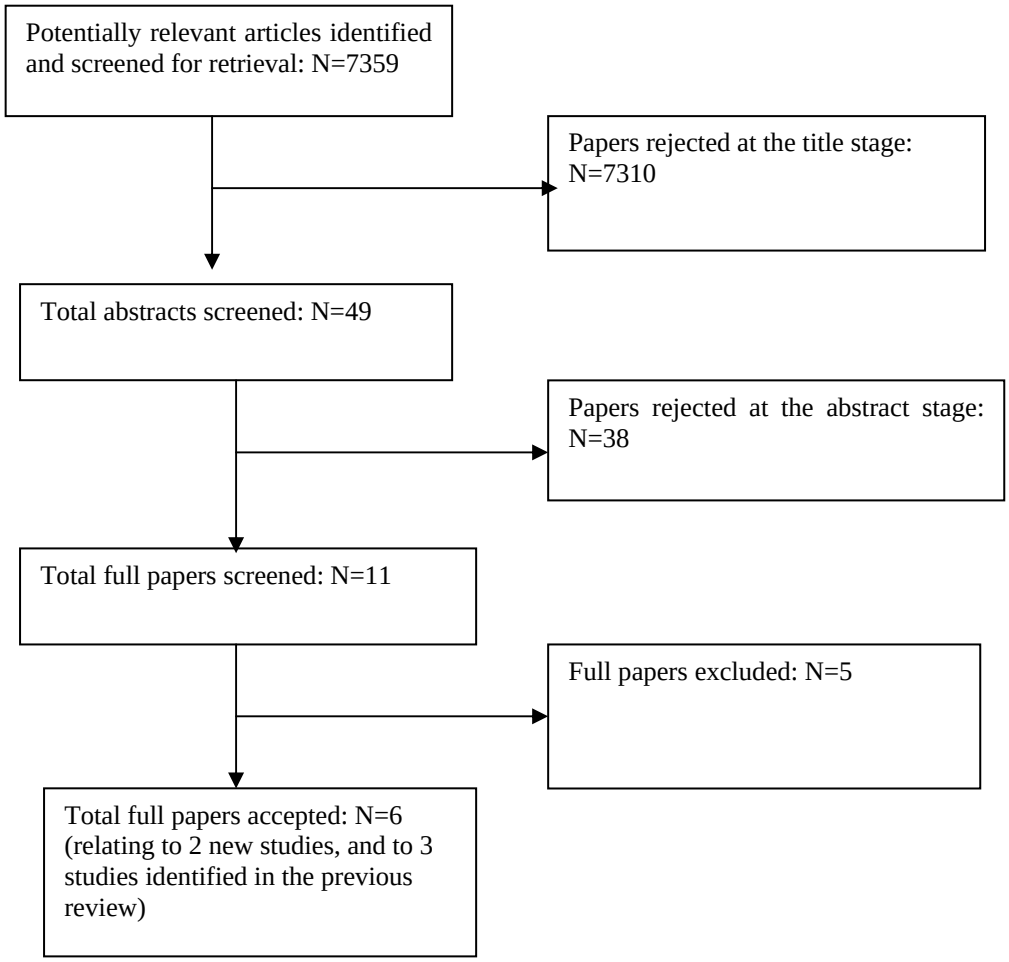
Comparators were limited to the following: placebo, no treatment, or direct comparison with one of the other included interventions.

Sifting, data extraction, quality assessment and meta-analysis were undertaken as in the original review.

Number of studies of clinical efficacy identified

The electronic literature searches identified 12,375 potentially relevant articles which were subsequent to those identified by the searches carried out in 2002. Six of these articles met the review inclusion criteria. Two of these reported new studies, and four presented additional relevant data relating to three studies which had been included in the original review (see Figure 1).

Figure 1: Summary of Study Selection and Exclusion: Electronic Literature Searches



Number and type of studies excluded, with reasons

Because so many articles were identified which did not meet the inclusion criteria, and were therefore excluded as part of the sifting process, details are given here only of those studies which were excluded at the full paper stage. These studies, and the reasons for their exclusion, are set out in Table 1.

Table 1: Excluded studies, with reasons for exclusion

Study	Reason for exclusion
Bone et al 2004 [51] (Extension of two 3-year multi-centre dose-ranging trials with identical designs, pooled data from which were published by Liberman et al in 1995.[52])	Lack of relevant comparator arm. After the initial 3-year period, the original placebo arm was given open-label alendronate for 2 years and then discharged from the study; the other 3 arms all received alendronate at varying doses for the original study and for all or part of the 7-year extension study (one arm received placebo for the last 5 years of the extension study).
Greenspan et al 2002 [53] (One-year extension of Bone et al 2000 [54])	Absence of relevant comparison since the original alendronate arm was reallocated to placebo. No fracture data were presented.
Greenspan et al 2003 [55]	The study exclusion criterion for BMD (femoral neck BMD of 0.9 g/cm^2 or greater) permitted the recruitment of women who did not have osteoporosis or osteopenia.
Kushida et al 2004 [56]	Participants included men.
McClung et al 2004 [57]	No fracture data were presented additional to those available to the original review.

Details of those studies that have been included are given in Appendix 2.

3.1 Efficacy data used in the model

One of the criteria for inclusion in the review was that the study participants were women with primary osteoporosis who were at least 6 months postmenopausal. This was therefore inclusive of osteoporosis, severe osteoporosis and osteopenia. Clinicians within the GDG believe that there is no plausible reason for fracture efficacy to be altered following a fracture. As such, efficacy data from women with severe osteoporosis is assumed to be equivalent to that in women with osteoporosis. The GDG also believe that in the absence of evidence showing a clear difference in efficacy between women with osteoporosis and osteopenia, the efficacy should be assumed to be the same for these two groups. We will therefore use one efficacy for all women regardless of their T-Score and this will be derived from trials including women with osteoporosis and women with osteopenia. The meta-analysed relative risks for each fracture type and for each intervention are presented in detail in Appendix 3.

Since fractures of the rib, sternum, scapula, tibia and fibula are now included with proximal humerus fractures, it was decided that the efficacy applicable to these fractures would be that taken from all non-vertebral fractures. It was assumed that the efficacy in reducing hip, pelvis and other femoral fractures would be equivalent to that for hip fractures alone.

The meta-analysed fracture efficacy data is summarised in Table 2 and the forest plots are given in Appendix 3. Where RRs have confidence intervals that span unity or where there was no data available, we have assumed no effect.

Table 2: RR of fracture for women with osteoporosis or osteopenia but no prior fracture. Assumes efficacy seen in women with osteoporosis, severe osteoporosis and osteopenia.

Drug	Vertebral	Hip, pelvis and other femoral fractures	Wrist	Proximal Humerus, rib, sternum, scapula, tibia and fibula fractures
Alendronate	0.56 (0.46 – 0.68)	0.62 (0.40 – 0.98)	Assumed no effect	0.81 (0.68 – 0.97)
Risedronate	0.61 (0.50 – 0.75)	0.74 (0.59 – 0.93)	Assumed no effect	0.76 (0.64 – 0.91)
Etidronate	0.40 (0.20 – 0.83)	Assumed no effect	Assumed no effect	Assumed no effect
Raloxifene	0.65 (0.53 – 0.79)	Assumed no effect	Assumed no effect	Assumed no effect

In addition to fracture reduction, raloxifene has been shown to reduce the incidence of breast cancer. RR 0.38 (0.24 – 0.58) [41]

Raloxifene has been shown to significantly increase the risk of venous thrombosis, [58] but also has been shown to reduce acute cardiovascular events in high risk women. [22] Due to the small absolute risk of venous thrombosis in women, and the non-significant effect on cardiovascular events for all women, neither effect was incorporated into the model.

Although observational data were available for etidronate, the GDG consensus was that only RCT evidence be used for estimates of efficacy.

In the absence of strong data, it has been assumed that these efficacies remain constant at all ages. There is however a paucity of data in the very elderly and this is noted as a caveat in the results produced for women aged 80 years and older.

In the absence of strong data, it has been assumed that these efficacies remain constant for all levels of T-Score.

APPENDIX 2. Relevant efficacy studies published since 2002.

Alendronate

No relevant studies were identified.

Etidronate

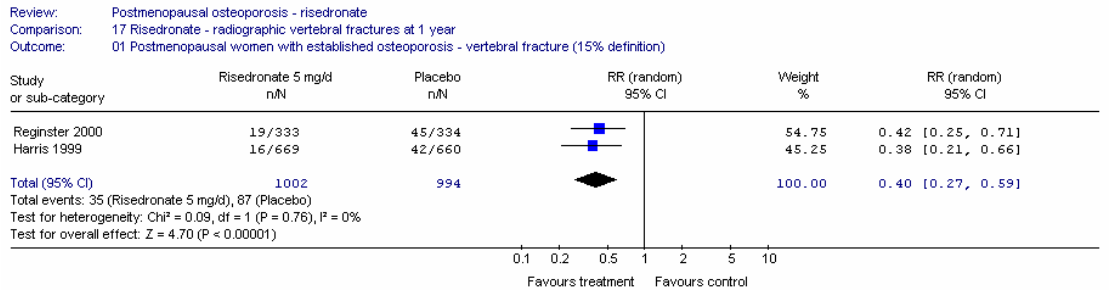
One relevant study was identified which was published subsequent to the original review. [76] This studied the effect of two years' treatment with a range of treatments, including cyclical etidronate (200 mg/d for 2 weeks followed by 10 weeks without medication), on postmenopausal Japanese women with osteoporosis or established osteoporosis. Eight of the 66 women in the etidronate group developed at least one new vertebral fracture, compared with 17 of the 16 in the control group (RR 0.47, 95% CI 0.22-1.01). One woman in the etidronate group suffered a forearm fracture; there were 3 nonvertebral fractures in the control group (1 femoral neck, 2 forearm); as the number of women in the control group who suffered fractures was not specified, the relative risk could not be calculated. Although the etidronate dose used is half the UK licensed dose, this is the normal dose for a Japanese population, however the women were not provided with supplementary calcium. Due to these reasons this study has been excluded from the meta-analysis.

Risedronate

Two articles were identified which presented additional data relating to studies included in the original review.

Roux et al [77] pooled previously unpublished data from two very similar 3-year studies: the VERT-MN [78] and VERT-NA [79] studies. These new data indicate that, relative to placebo, treatment with 5 mg risedronate is associated with a reduction in the risk of clinical vertebral fracture after as little as 6 months (RR 0.08 (95% CI 0.01-0.63) at 6 months, and 0.31 (95% CI 0.12-0.78) at one year) (investigators' calculations). [77] Data were not available on radiographic vertebral fractures at 6 months, and the data provided at one year (33 women with radiographic fractures in the risedronate 5 mg group and 86 in the placebo group) were slightly different from those available from the original study publications. Roux et al did not calculate the relative risk of radiographic fracture at one year, and it was not possible to do so from the data they provided, as they did not indicate the number of women for whom radiographs were available. As such this has been excluded from the meta-analyses. However, meta-analysis of the data provided in the original study publications yielded a relative risk of radiographic vertebral fracture at one year which was not incompatible with the relative risk of clinical vertebral fracture at one year calculated by Roux et al (see Figure 2).

Figure 2: **Radiographic vertebral fracture: effect of one year's treatment with risedronate 5 mg**



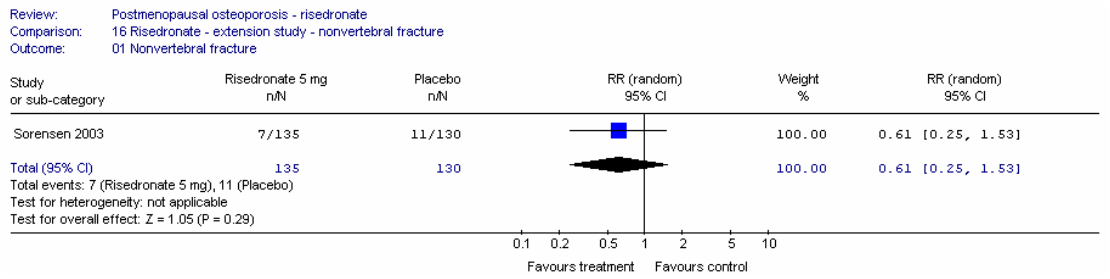
Sorensen et al [80] described a two-year extension to the three-year VERT-MN study. Of the 814 women who entered the original study, 472 completed the full three years. Because some centres did not continue in the extension study, only 292 of the 472 study completers were invited to participate in it, and only 265 of that 292 (33% of the original participants) agreed to do so. As so few participants were retained in the extension study, it could be argued that the effect of randomisation has been largely lost. However, data are presented to indicate that, at entry to the extension study, the groups were still comparable in terms of a limited number of characteristics.

During the two-year extension period, 15 women (13.8%) in the risedronate group and 29 women (28.2%) in the placebo group experienced new vertebral fractures. As no information was given regarding the number of women in each group for whom radiographs were available, it was not possible to calculate the relative risk of fracture. However, the authors stated that risedronate treatment reduced the risk of new vertebral fracture over this period by 59% (95% CI 19-79%, P=0.01). [80] Although the numbers of women who fractured were known, the numbers for whom radiographs were available were unknown. Additionally because so few of the original women were retained in the extension study the effect of randomisation was weakened. Due to these reasons the study was omitted from our meta-analysis.

Eleven women in the placebo group and 7 in the risedronate group experienced an osteoporosis-related nonvertebral fracture during the 2-year extension period; no significant difference was seen between the two treatment groups (see Figure 3). The most common fracture site was the humerus, occurring in 6 women in the placebo group and 3 in the risedronate group; there were no hip fractures.

No information was given regarding the number of women in each treatment group who suffered either vertebral or nonvertebral fracture over the whole five-year period of the original study plus the extension.

Figure 3: **VERT-MN study two-year extension: nonvertebral fracture**



Raloxifene

One new study was identified which examined the additive effect of raloxifene, compared with placebo, in women with a femoral neck T score of –2.0 or lower, with or without prior fracture, who were also receiving fluoride, calcium and vitamin D [81] The study was not large enough do demonstrate a statistically significant reduction in terms of either vertebral or nonvertebral fracture (see Figure 4 and Figure 5). Because of the use of fluoride as a co-intervention, these results have not been included in a meta-analysis.

Figure 4: Raloxifene: vertebral fracture

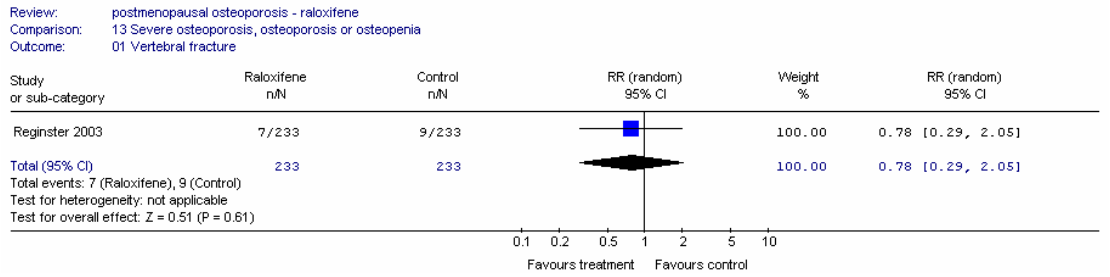
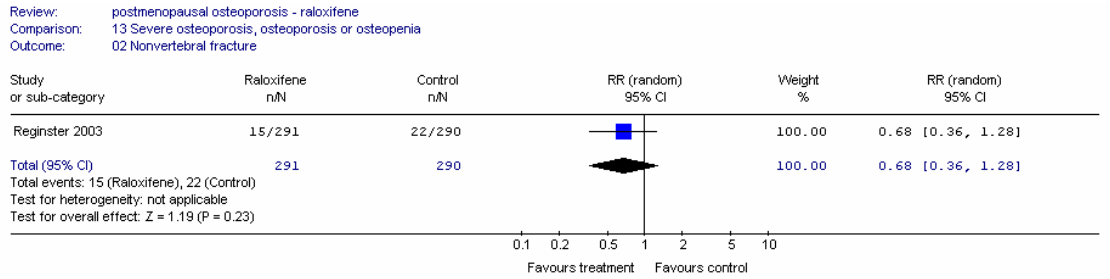


Figure 5: **Raloxifene: nonvertebral fracture**



In addition, two articles were identified which presented new data relating to the MORE study. One article [82] examined data relating to study participants who did not have vertebral fracture at study entry, and who were randomised to either the 60 mg dose of raloxifene or to placebo. This undertook subgroup analyses of the effect of raloxifene on vertebral fracture in women with osteoporosis and those with osteopenia.

The MORE study inclusion criteria required all participants to have either vertebral fracture at study entry or osteoporosis, defined as a T-score of –2.5 or less at the lumbar spine or femoral neck. Of the 5115 women in the 60 mg and placebo arms for

whom a baseline radiograph was available, 1911 (37%) had at least one vertebral fracture at study entry. However, 2557 of the remaining 3204 had osteopenia, defined as a total hip BMD T-score of over –2.5, and only 635 had osteoporosis, defined as a total hip BMD T-score of –2.5 or less; baseline total hip BMD T-scores were not available for the remaining 12 women without prevalent vertebral fracture. [82]

The subgroup analysis indicated that raloxifene significantly reduced the risk of radiographic vertebral fracture in women with osteopenia (see Figure 6) as well as in those with osteoporosis without prior fracture (see

Figure 7). However, it should be borne in mind that randomisation was not stratified by T-score, and therefore the subgroup analyses are not true randomised comparisons.

Figure 6 Raloxifene: women with osteopenia: vertebral fracture

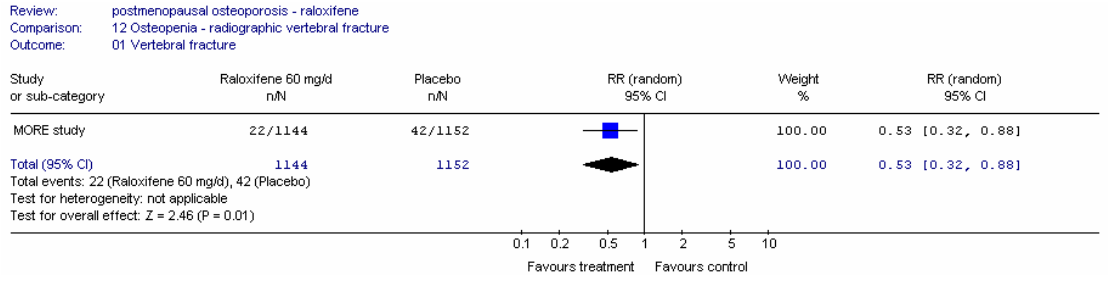
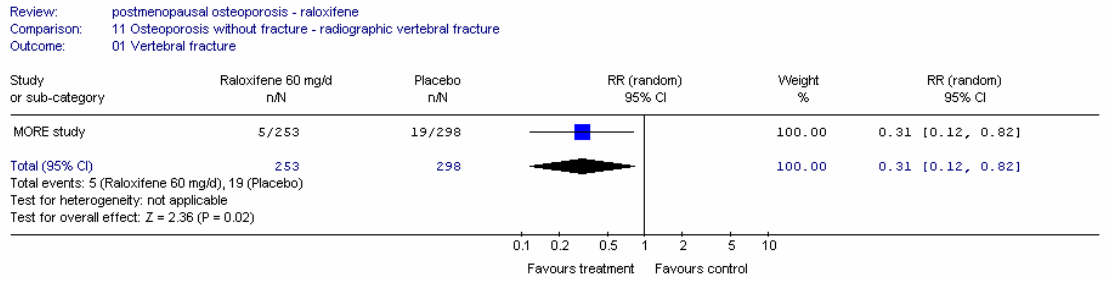


Figure 7 Raloxifene: women with osteoporosis without fracture: vertebral fracture



The second article [83] reported the effect of raloxifene on new vertebral fractures according to the severity of those fractures (mild-only or moderate/severe). This study was found in abstract form only and without the numbers of women who fractured or who did not fracture during the study.

Since both articles had come from the MORE study, the results from neither were included in the meta-analysis.

APPENDIX 3

A 3.1 Efficacy in women with osteoporosis or osteopenia

The figures below present the meta-analysed relative risks for vertebral, hip, wrist and non-vertebral fracture types for each intervention. Inclusion criteria were trials in women with osteoporosis and osteopenia and with fracture as an outcome measure. These relative risks will be assumed applicable to all women.

Alendronate

Figure 8: RR of vertebral fracture: alendronate versus controls for osteoporosis and osteopenia

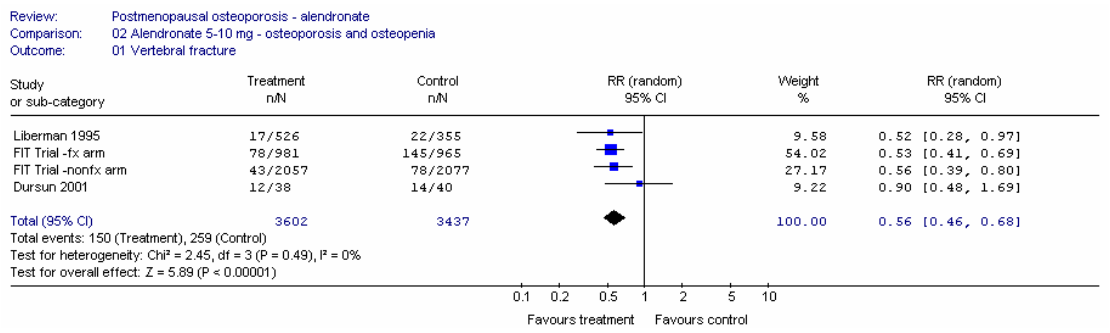


Figure 9: RR of hip fracture: alendronate versus controls for osteoporosis and osteopenia

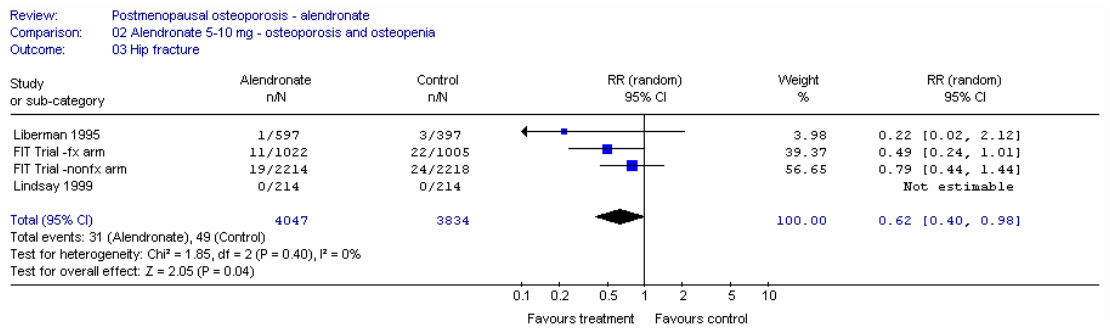
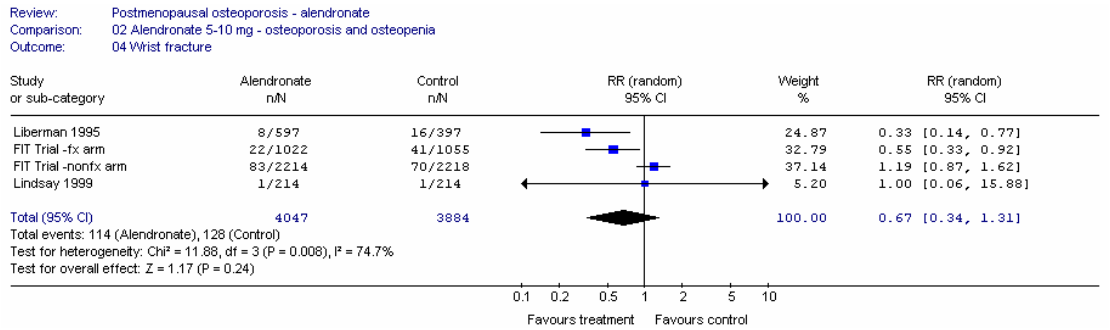
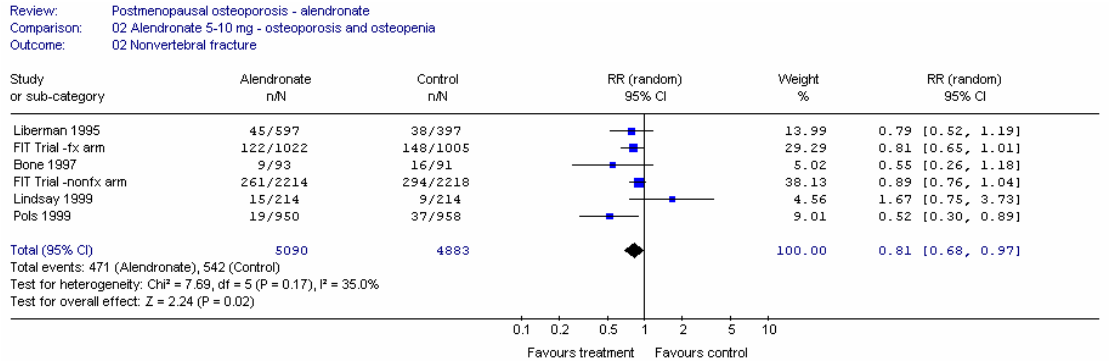


Figure 10: RR of wrist fracture: alendronate versus controls for osteoporosis and osteopenia



As the efficacy value crossed unity we have assumed that alendronate has no effect on wrist fracture.

Figure 11: RR of non-vertebral fracture: alendronate versus controls for osteoporosis and osteopenia



Etidronate

Figure 12: RR of vertebral fracture: etidronate versus controls for osteoporosis and osteopenia

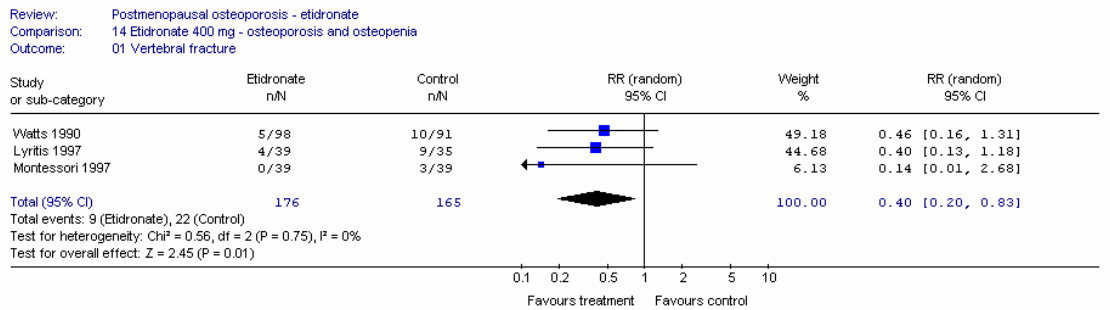
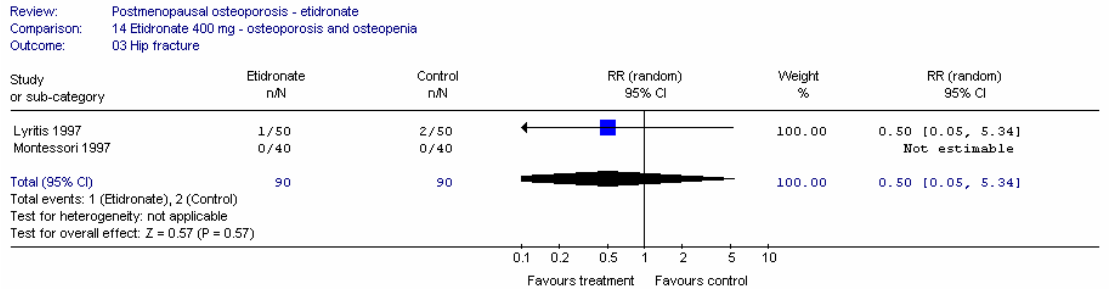


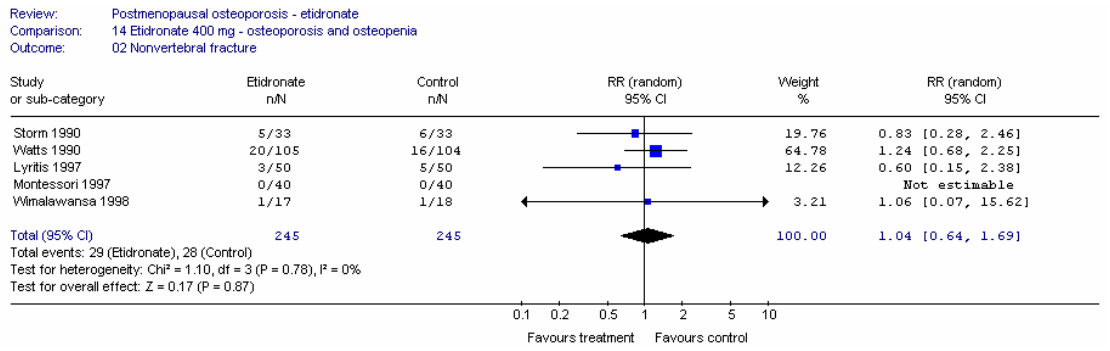
Figure 13: RR of hip fracture: etidronate versus controls for osteoporosis and osteopenia



Due to the large confidence intervals spanning unity for RR of hip fracture it was assumed that etidronate has no effect on hip fracture.

Wrist fracture – no data

Figure 14: RR of hip fracture: etidronate versus controls for osteoporosis and osteopenia



As the efficacy value crossed unity we have assumed that etidronate has no effect on wrist fracture.

Risedronate

Figure 15: RR of vertebral fracture: risedronate versus controls for osteoporosis and osteopenia

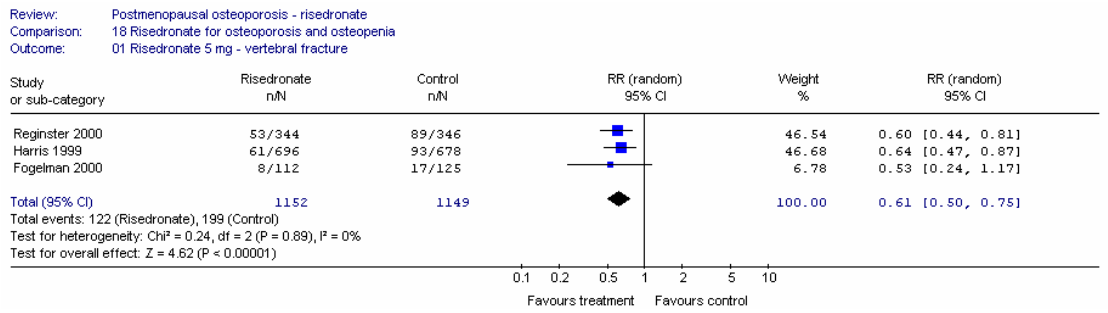
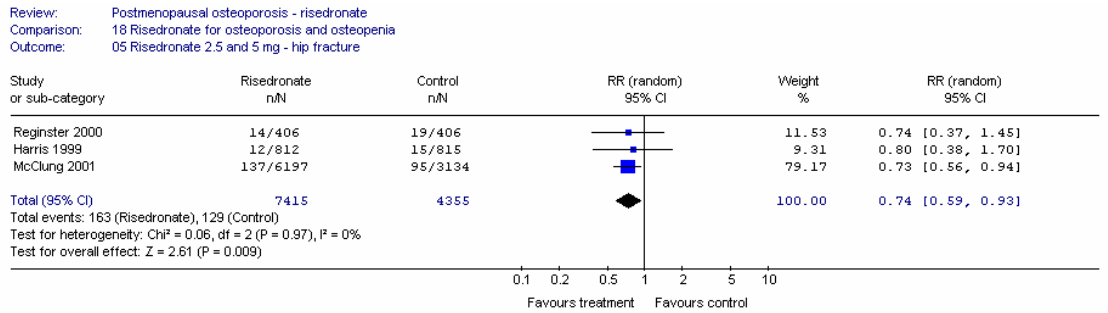
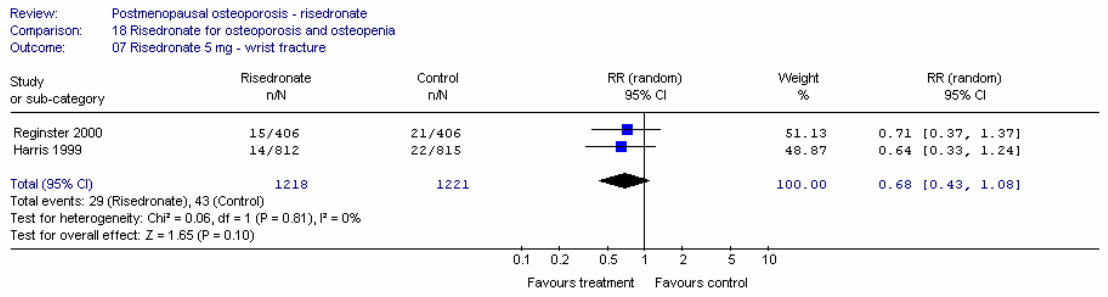


Figure 16: RR of hip fracture: risedronate versus controls for osteoporosis and osteopenia



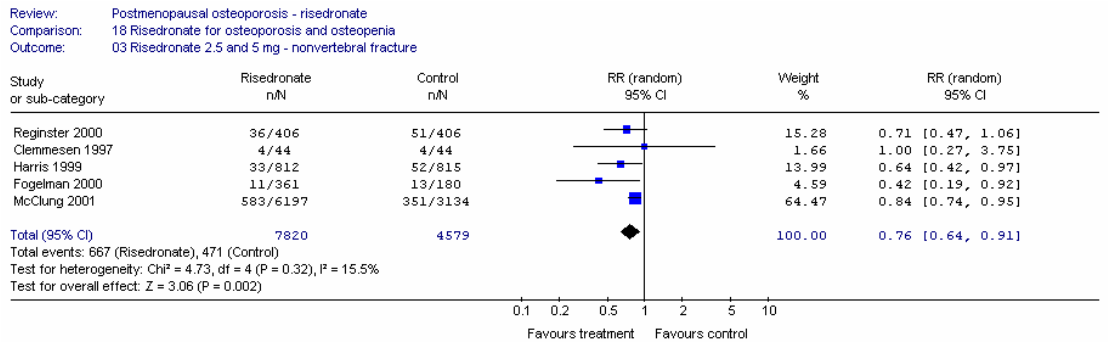
The dose of risedronate has been analysed for 2.5mg and 5mg, as this includes the large McClung study. Excluding this study resulted in Risedronate having no significant effect at the hip.

Figure 17: RR of wrist fracture: risedronate versus controls for osteoporosis and osteopenia



As the efficacy value crossed unity we have assumed that etidronate has no effect on wrist fracture.

Figure 18: RR of proximal humerus fracture: risedronate versus controls for osteoporosis and osteopenia



In order to be compatible with hip fracture data, the dose of Risedronate includes both 2.5mg and 5mg. Data from Clemmesen was from the continuous Risedronate arm.

Raloxifene

Vertebral fracture: the Lufkin and MORE studies used different fracture definitions, and it did not seem appropriate to combine their results by meta-analysis, so instead we used the results from the MORE study which was larger and better quality. This gave a relative risk of incident vertebral fracture in women receiving a 60 mg daily dose of raloxifene of 0.65 (95% CI 0.53-0.79) in women, and 0.54 (95% CI 0.44-0.67) in those receiving a 120 mg dose. The UK licensed dose is 60mg and this dose is reported for vertebral fractures. For hip, wrist and all non-vertebral fractures only pooled data for 60mg and 120mg were available

Figure 19: RR of vertebral fracture: raloxifene (60mg daily dose) versus controls for osteoporosis and osteopenia

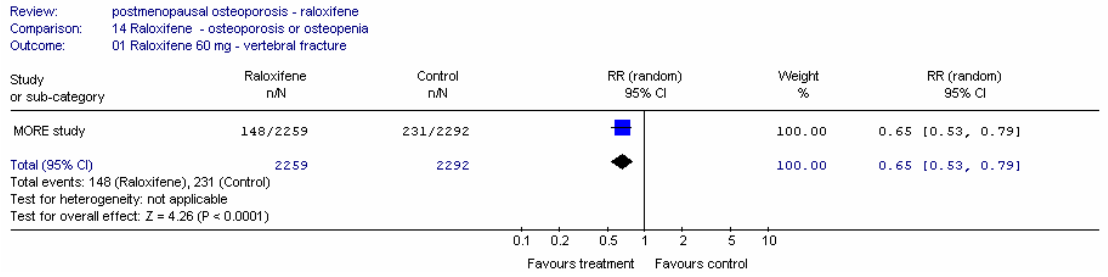
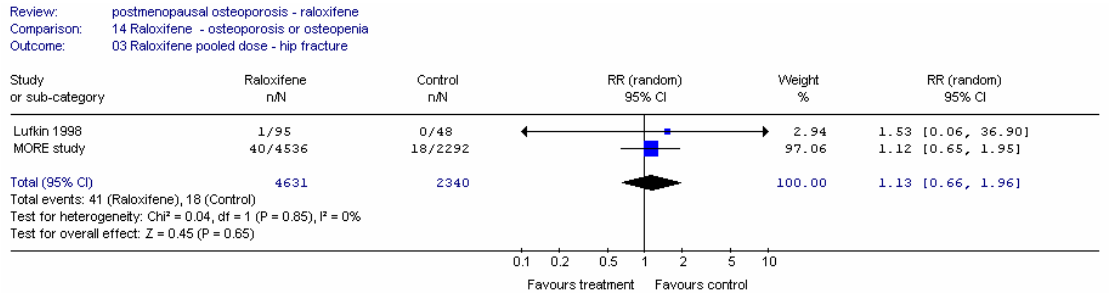
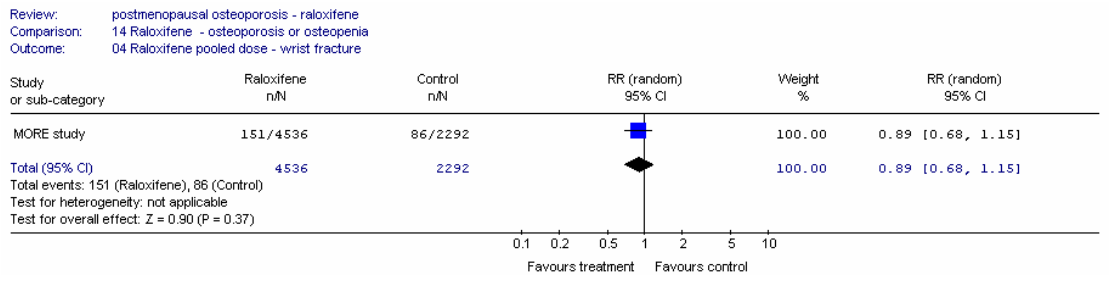


Figure 20: RR of hip fracture: raloxifene versus controls for osteoporosis and osteopenia



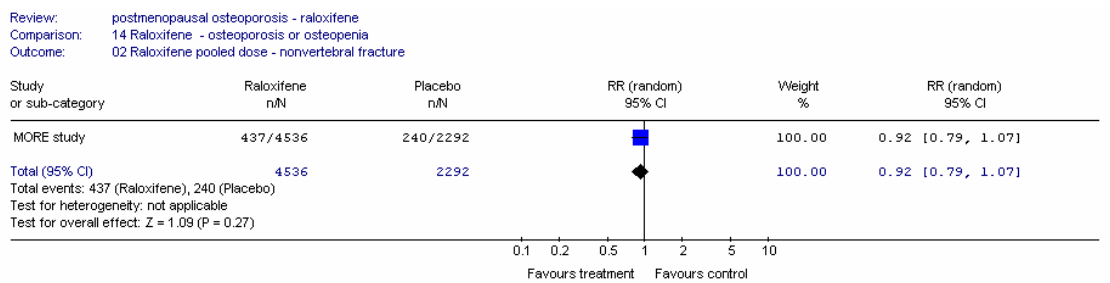
Due to the wide confidence intervals spanning unity we have assumed no effect at the hip.

Figure 21: RR of wrist fracture: raloxifene versus controls for osteoporosis and osteopenia



Due to the wide confidence intervals spanning unity we have assumed no effect at the wrist.

Figure 22: RR of non-vertebral fracture: raloxifene versus controls for osteoporosis and osteopenia



Due to the wide confidence intervals spanning unity we have assumed no effect on non-vertebral fractures.