Fracture prevention in postmenopausal women

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Olivier Bruyere, John Edwards, and Jean-Yves Reginster

<table>
<thead>
<tr>
<th>QUESTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of treatments to prevent fractures in postmenopausal women. 1188</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beneficial</td>
</tr>
<tr>
<td>Alendronate .......................... 1188</td>
</tr>
<tr>
<td>Calcitonin (in women with osteoporosis) .......................... 1193</td>
</tr>
<tr>
<td>Calcium plus vitamin D .......................... 1191</td>
</tr>
<tr>
<td>Hip protectors .......................... 1196</td>
</tr>
<tr>
<td>Likely to be beneficial</td>
</tr>
<tr>
<td>Etidronate .......................... 1188</td>
</tr>
<tr>
<td>Pamidronate .......................... 1188</td>
</tr>
<tr>
<td>Risedronate .......................... 1188</td>
</tr>
<tr>
<td>Unknown effectiveness</td>
</tr>
<tr>
<td>Environmental manipulation .......................... 1194</td>
</tr>
<tr>
<td>Exercise .......................... 1195</td>
</tr>
<tr>
<td>Tiludronate .......................... 1190</td>
</tr>
<tr>
<td>Unlikely to be beneficial</td>
</tr>
<tr>
<td>Calcium alone (in people without previous fracture) .......................... 1191</td>
</tr>
<tr>
<td>Vitamin D alone .......................... 1191</td>
</tr>
<tr>
<td>Likely to be ineffective or harmful</td>
</tr>
<tr>
<td>Hormone replacement therapy .......................... 1198</td>
</tr>
<tr>
<td>To be covered in future updates</td>
</tr>
<tr>
<td>Prevention of pathological fractures</td>
</tr>
<tr>
<td>Effects of dietary intervention</td>
</tr>
<tr>
<td>Effects of helmets</td>
</tr>
<tr>
<td>Effects of joint and limb pads</td>
</tr>
<tr>
<td>See glossary, p 1200</td>
</tr>
</tbody>
</table>

Key Messages

- **Alendronate** One systematic review and one subsequent RCT have found that alendronate reduces vertebral and non-vertebral fractures over 1–4 years compared with placebo.

- **Calcitonin** One large RCT found that calcitonin versus placebo significantly reduced new vertebral fractures over 5 years. One systematic review combined evidence from RCTs in men and women who were taking corticosteroids or had osteoporosis or previous fracture. In this heterogeneous population, it found limited evidence that calcitonin non-significantly reduced vertebral or non-vertebral fracture rates compared with placebo, no treatment, calcium, or calcium plus vitamin D.

- **Calcium alone** One RCT in women with existing fractures found that calcium versus placebo reduced new vertebral or non-vertebral fractures over 3 years, but found no significant difference in new fractures in women without existing fractures. Another RCT found no significant difference with calcium versus placebo in the proportion of women who had one or more new fractures over 2–4 years.

- **Calcium plus vitamin D** One large RCT in elderly women in nursing homes has found that calcium plus vitamin D3 versus placebo significantly reduces non-vertebral fractures over 18 months to 3 years. Two smaller RCTs found no significant difference in vertebral fractures over 2–3 years with calcium plus vitamin D3 versus placebo, but they may have lacked power to exclude a clinically important difference.

Fracture prevention in postmenopausal women

- **Environmental manipulation; exercise** RCTs found insufficient evidence about the effects of these interventions in preventing vertebral and non-vertebral fractures.

- **Etidronate** One systematic review has found that etidronate versus placebo, calcium, or calcium plus vitamin D reduces vertebral fractures over 2 years. One systematic review has found no significant difference in non-vertebral fractures over 2 years with etidronate versus placebo, calcium, or calcium plus vitamin D.

- **Hip protectors** RCTs in elderly residents of nursing homes found that hip protectors versus no hip protectors significantly reduced hip fractures over 9–19 months, but found no significant difference in pelvic fractures. One RCT in people aged over 65 years in institutional care found that a multifactorial intervention (including staff education, environmental manipulation, exercise, walking aids, drug regimen reviews, and hip protectors for those considered at higher risk) versus usual care reduced hip fractures over 34 weeks.

- **Hormone replacement therapy** RCTs found no consistently significant effect of hormone replacement therapy on vertebral fracture. One systematic review and one subsequent RCT found that hormone replacement therapy versus placebo, no treatment, calcium, or calcium plus vitamin D reduced non-vertebral fracture rate. However, another large subsequent RCT found no significant difference in non-vertebral fractures with hormone replacement therapy versus placebo. Another large RCT, comparing oestrogen plus progestin versus placebo in healthy postmenopausal women, was stopped because hormonal therapy increased risks of invasive breast cancer, coronary events, stroke, and pulmonary embolism.

- **Pamidronate** One RCT found that pamidronate versus placebo reduced new vertebral fractures after 3 years, but another small RCT found no significant difference with pamidronate versus placebo in vertebral fracture rate.

- **Risedronate** Two large RCTs in women with previous fractures have found that risedronate versus placebo significantly reduces new vertebral fractures over 3 years. One of the RCTs found that risedronate versus placebo reduced non-vertebral fractures over 3 years, but the other found no significant difference. One large RCT in women aged over 70 years has found that risedronate versus placebo reduces hip fractures over 3 years. Observational evidence suggests that risedronate may be associated with increased pulmonary cancer.

- **Tiludronate** One RCT in women with low bone mineral density with or without previous fractures found no significant difference with tiludronate versus placebo in vertebral fractures over 3 years, but it may have lacked power to detect a clinically important difference.

- **Vitamin D** One large RCT identified by a systematic review and one large subsequent RCT found no significant difference with vitamin D3 versus placebo in non-vertebral fractures over 3 years. One systematic review found limited evidence from two small RCTs that calcitriol versus placebo reduced vertebral fractures over 3 years.

**DEFINITION** A fracture is a break or disruption of bone or cartilage. Symptoms and signs may include immobility, pain, tenderness, numbness, bruising, joint deformity, joint swelling, limb deformity, and limb shortening. Diagnosis is usually based on a typical clinical picture combined with results from an appropriate imaging technique.

**INCIDENCE** The lifetime risk of fracture in white women is 20% for the spine, 15% for the wrist, and 18% for the hip.
Fracture prevention in postmenopausal women

AETIOLOGY/ RISKS Fractures usually arise from trauma. Risk factors include those associated with an increased risks of falling (such as ataxia, drug and alcohol intake, loose carpets), age, osteoporosis, bony metases, and other bone disorders.

PROGNOSIS Fractures may result in pain, short or long term disability, haemorrhage, thromboembolic disease (see thromboembolism, p 246), shock, and death. Vertebral fractures are associated with pain, physical impairment, muscular atrophy, changes in body shape, loss of physical function, and lower quality of life. About 20% of women die in the first year after a hip fracture, representing an increase in mortality of 12–20% compared with women of similar age and no hip fracture. Half of elderly women who had been independent become partly dependent after hip fracture. A third become totally dependant.

AIMS To prevent fractures, with minimal adverse effects from treatment.

OUTCOMES Incidence of hip, wrist, and vertebral fractures.

METHODS Clinical Evidence search and appraisal September 2002. We also hand searched journals of bone diseases and carried out manual searches using the bibliographies of review articles published after 1985. Some of the RCTs identified provide results generalised to fracture per person/year or overall fractures. These results provide an idea of the group effect of an intervention, but not of its effects on the incidence of fracture in an individual. Data on multiple fractures in one person clearly differ from data on multiple people experiencing a single fracture. Regulatory authorities and scientific groups have recommended that the results of studies evaluating new interventions are expressed in terms of the proportion of people experiencing new fractures.

QUESTION What are the effects of treatments to prevent fractures in postmenopausal women?

OPTION BISPHONONATES

Olivier Bruyere and Jean-Yves Reginster

One systematic review and one subsequent RCT have found that alendronate versus placebo significantly reduces vertebral and non-vertebral fractures over 1–4 years. One systematic review has found that etidronate versus placebo, calcium, or calcium plus vitamin D significantly reduces vertebral fractures over 2 years, but has found no significant difference in non-vertebral fractures. One RCT found that pamidronate versus placebo significantly reduced new vertebral fractures after 3 years, but another small RCT found no significant difference with pamidronate versus placebo in vertebral fracture rate. Two large RCTs in women with previous fractures have found that risedronate versus placebo significantly reduces new vertebral fractures over 3 years. One of the RCTs found that risedronate versus placebo reduced non-vertebral fractures over 3 years, but the other found no significant difference. One large RCT in women aged over 70 years has found that risedronate versus placebo significantly reduces hip fractures over 3 years. Observational evidence suggests that risedronate may be associated with significant
Fracture prevention in postmenopausal women

increase in pulmonary cancer. One RCT in women with low bone mineral density with or without previous fractures found that tiludronate versus placebo reduced non-vertebral fractures. It found no significant difference with tiludronate versus placebo in vertebral fractures over 3 years, but it may have lacked power to detect a clinically important difference.

Benefits: **Alendronate:** We found one systematic review and one subsequent RCT. The systematic review (search date 1998, 7 RCTs, 10,287 postmenopausal women aged 39–85 years) found that alendronate versus placebo significantly reduced vertebral fractures (fractures confirmed radiologically; 4 RCTs; RR 0.54, 95% CI 0.45 to 0.66) and non-vertebral fractures (6 RCTs; RR 0.81, 95% CI 0.72 to 0.92). It found that fewer people had hip fractures over 1–4 years, but the difference was not significant (3 RCTs; RR 0.64, 95% CI 0.40 to 1.01; results presented graphically). One large subsequent RCT (3658 women with existing vertebral fracture or osteoporosis) compared alendronate (5–10 mg/day) versus placebo for 3–4 years. It found that alendronate versus placebo significantly reduced new non-vertebral fractures, including hip fractures, over 3 years (all non-vertebral: RR 0.73, 95% CI 0.61 to 0.87; hip: RR 0.47, 95% CI 0.20 to 0.79; no further data provided) and both clinical and radiological vertebral fractures over 3 years (radiological vertebral: RR 0.52, 95% CI 0.42 to 0.66; no further data provided). **Etidronate:** We found one systematic review (search date 1998, 13 RCTs, 10,107 women) comparing etidronate versus placebo, calcium, or calcium plus vitamin D. It found that etidronate versus placebo significantly reduced vertebral fractures over 2 years (9 RCTs: 32/538 [6%] v 54/538 [10%]; RR 0.60, 95% CI 0.41 to 0.88), but found no significant difference in non-vertebral fractures (7 RCTs: 48/433 [11%] v 49/434 [11%]; RR 0.98, 95% CI 0.68 to 1.42). The review did not describe clearly how fractures were diagnosed. **Pamidronate:** We found no systematic review but found two RCTs comparing pamidronate (150 mg/day) versus placebo. The first RCT (101 people, including 78 postmenopausal women) found that pamidronate significantly reduced new radiologically confirmed vertebral fractures after 3 years (5/46 [11%] with pamidronate v 15/45 [33%] with placebo; RR 0.33, 95% CI 0.14 to 0.77). The second RCT found no significant difference after 2 years with pamidronate versus placebo in vertebral fractures (fractures confirmed radiologically; 13/100 [13%] person years with pamidronate v 24/100 [24%] person years with control; P = 0.07; see methods, p 1186). However, it may have been too small to exclude a clinically important difference. **Risedronate:** We found no systematic review but found three RCTs. The first RCT (2458 women < 85 years with at least 1 vertebral fracture) compared oral risedronate (2.5 or 5.0 mg/day) versus placebo for 3 years. After 1 year the 2.5 mg dose of risedronate was discontinued as 5 mg was found to be more effective. It found that risedronate 5 mg versus placebo significantly reduced new vertebral fractures over 3 years (fractures confirmed radiologically; 61/696 [11.3%] with risedronate v 93/678 [13.6%] with placebo; RR 0.59, 95% CI 0.43 to 0.82) and non-vertebral fractures (33/812 [5.2%] with risedronate v 52/815 [6.4%] with placebo; RR 0.60, 95% CI 0.39 to 0.94; see comment below).
Fracture prevention in postmenopausal women

The second RCT (1226 women with 2 or more existing vertebral fractures) compared risendronate 2.5 or 5.0 mg daily versus placebo for 3 years. After 2 years, the 2.5 mg dose of risendronate was discontinued as 5 mg was more effective. It found that risendronate 5 mg versus placebo significantly reduced the proportion of women with new vertebral fractures over 3 years (fractures confirmed radiologically; 53/344 [18.1%] v 89/346 [29.0%]; RR 0.51, 95% CI 0.36 to 0.73; see comment below), but found no significant difference in the proportion of women with osteoporosis related non-vertebral fractures (36/406 [10.9%] with risendronate v 51/406 [16.0%] with placebo; RR 0.67, 95% CI 0.44 to 1.04; see comment below). The third RCT (9331 women > 70 years) compared risendronate 2.5 or 5.0 mg versus placebo. It found that risendronate significantly reduced the proportion of women who had hip fracture over 3 years (fractures confirmed radiologically; 137/6197 (2.8%) with risendronate v 95/3134 (3.9%) with placebo; RR 0.7, 95% CI 0.6 to 0.9; see comment below). Tildrakizumab: We found no systematic review. We found one RCT (1805 women with low vertebral bone mineral density and at least 1 existing vertebral fracture and 488 women with low bone mineral density and no existing fracture) comparing tildrakizumab 50 or 200 mg daily versus placebo for the first 7 days of each month for 3 years. It found no significant difference with tildrakizumab versus placebo in vertebral fractures over 3 years, but it may have been too small to detect a clinically important difference (fractures confirmed radiologically; 20% with tildrakizumab 50 mg v 19% with placebo; RR of a fracture 1.08, 95% CI 0.81 to 1.35; 19.2% with tildrakizumab 200 mg v 18.9% with placebo; RR of a fracture 1.01, 95% CI 0.75 to 1.27). It found that tildrakizumab 200 mg daily versus tildrakizumab 50 mg daily or versus placebo reduced non-vertebral fractures (6% with tildrakizumab 200 mg/day v 9% with tildrakizumab 50 mg v 12% with placebo; no further data provided).

Harms:

Alendronate: Observational evidence suggests that oral alendronate is associated with esophageal erosions and ulcerative esophagitis. However, one RCT identified by the review (where people took alendronate with 180–240 mL water on rising in the morning and remained upright for at least 30 min after swallowing the tablet and until they had eaten something) found no significant difference in esophagitis with alendronate versus placebo.

Risedronate: One observational study found limited evidence suggesting that the gastrointestinal safety of risedronate seems to be in the same range as alendronate. One non-systematic review (10 phase III studies) found limited evidence that risedronate versus placebo may be associated with a significant increase in the occurrence of pulmonary cancer (3.9/1000 people/year of exposure with risedronate 2.5 mg/day v 1.9/1000 people/year of exposure with risedronate 5.0 mg/day v 1.2/1000 people/year of exposure with placebo; significance not stated; see comment below).

Comment: Risedronate: Proportions in the RCTs were calculated based on the Kaplan-Meier survival curve. In the third RCT, risedronate versus placebo reduced hip fractures by 60% in women aged 70–79 years with osteoporosis and baseline vertebral fractures. However, this subgroup included only 1128/6197 women in the
Fracture prevention in postmenopausal women

trial and, although the RCT found an overall 30% reduction in the relative risk of hip fracture, this reduction was not significant either in women aged 70–79 years without existing vertebral fracture or in women over the age of 80 years with at least one clinical risk factor for hip fracture.16 The non-systematic review assessing the harms of risendronate16 did not provide a source of reference and the methods of the phase III studies identified are unclear. Pamidronate: Although one of the RCTs included both men and women at risk of hip fracture,6 it is likely that the results are generalisable to postmenopausal women.

OPTION | CALCIUM AND VITAMIN D ALONE OR IN COMBINATION

Olivier Bruyere and Jean-Yves Reginster

One RCT in women with existing fractures found that calcium versus placebo significantly reduced new vertebral or non-vertebral fractures over 3 years, but found no significant difference in new fractures in women without existing fractures. Another RCT found no significant difference with calcium versus placebo in the proportion of women who had one or more new fractures over 2–4 years. One large RCT identified by a systematic review and one large subsequent RCT found no significant difference with vitamin D3 versus placebo in non-vertebral fractures over 3 years. One systematic review found limited evidence from two small RCTs that calcitriol versus placebo significantly reduced vertebral fractures over 3 years. One large RCT in elderly women in nursing homes has found that calcium plus vitamin D3 versus placebo significantly reduces non-vertebral fractures over 18 months to 3 years. Two smaller RCTs found no significant difference in vertebral fractures over 2–3 years with calcium plus vitamin D3 versus placebo, but they may have lacked power to exclude a clinically important difference.

Benefits: Calcium versus placebo: We found no systematic review but found two RCTs.17,18 The first RCT (78 women) comparing calcium (calcium lactate–gluconate plus calcium carbonate, 1 g/day) versus placebo found no significant difference in the proportion of women who had one or more new fractures over 2–4 years, but it may have been too small to exclude a clinically important difference (symptomatic fractures confirmed radiologically; 2/38 [5%] v 7/40 [18%]; RR 0.30, 95% CI 0.06 to 1.36).17 The second RCT (197 women) compared oral calcium carbonate (1.2 g/day) versus placebo for a mean 3 years in women aged over 60 years with or without existing fractures (see comment below).18 It found that in women with existing fractures (94 women, mean age 74.9 years), calcium versus placebo significantly reduced vertebral and non-vertebral fractures over a mean of 3 years (fracture confirmed by x-ray; 15/53 [28%] v 21/41 [51%]; RR 0.55, 95% CI 0.33 to 0.93), but found no significant difference in vertebral and non-vertebral fractures in women without existing fractures (103 women; mean age 72.4; 12/42 [29%] with calcium v 13/61 [21%] with placebo; RR 1.34, 95% CI 0.68 to 2.64).18 Vitamin D3 versus placebo: We found one systematic review (search date 2000, 1 RCT)19 and one subsequent RCT.20 The RCT identified by the review (2578 people; 1916 women, 662 men, mean age 80 years, living at home; see comment below) found no significant difference with vitamin D3 versus placebo in hip fracture (confirmed by clinical assessment
Fracture prevention in postmenopausal women

and x ray films; 58/1284 [4.5%] v 48/1280 [3.7%]; RR 1.20, 95% CI 0.83 to 1.75) or any non-vertebral fracture over 3 years (135/1284 [11%] v 122/1280 [10%]; RR 1.10 95% CI 0.87 to 1.39).

The subsequent RCT (1144 people resident in nursing homes, 75% were women) found no significant difference with vitamin D3 (10 μg/day) versus placebo in hip fracture or any non-vertebral fracture (fractures confirmed by hospital discharge letter or x ray film) after 2 years' treatment (hip fracture: 50/569 [8.8%] with vitamin D v 47/575 [8.2%] with control; RR 1.09, 95% CI 0.73 to 1.63; non-vertebral fracture: 69/569 [12.1%] with vitamin D v 76/575 [13.2%] with placebo; RR 0.92, 95% CI 0.66 to 1.27).20

Vitamin D analogue (calcitriol) versus placebo: The systematic review19 also identified two small RCTs (68 women aged ≥ 54 years) comparing calcitriol (1.25 dinydroxy vitamin D) versus placebo. It found that calcitriol versus placebo significantly reduced new vertebral fractures over 3 years (fractures confirmed radiologically; 8/34 [23%] with calcitriol v 17/34 [50%] with placebo; RR 0.49, 95% CI 0.25 to 0.95). Vitamin D analogue (calcitriol) versus calcium: The systematic review19 also identified one RCT (622 postmenopausal women aged 50–79 years with one or more radiologically confirmed existing fracture)21 comparing calcitriol versus calcium (see comment below). It found that calcitriol significantly reduced new vertebral fractures during the third year of treatment (12/213 [6%] with calcitriol v 44/219 [20%] with placebo; RR 0.28, 95% CI 0.15 to 0.52; see comment below).19 The RCT did not have a central x ray reading facility for the assessment of vertebral fractures.21 Calcium plus vitamin D3 versus placebo: We found one systematic review (search date 2000, 2 RCTs, 3715 people)19 and one subsequent RCT.22 One of the RCTs identified by the review (3270 mobile elderly women, aged 69–106 years, living in nursing homes) found that calcium plus vitamin D3 versus placebo significantly reduced hip fractures (80/1387 [6%] with calcium plus vitamin D3 v 110/1403 [8%] with placebo; RR 0.74, 95% CI 0.60 to 0.91) and all non-vertebral fractures (160/1387 [11%] with calcium plus vitamin D3 v 215/1403 [15%] with placebo; RR 0.75, 95% CI 0.62 to 0.91) over 18 months. This difference remained significant after 3 years' treatment (hip fracture: 137/1176 [12%] with calcium plus vitamin D3 v 178/1127 [16%] with placebo; RR 0.74, 95% CI 0.60 to 0.91; all non-vertebral fracture: 255/1176 [22%] with calcium plus vitamin D3 v 308/1127 [27%] with placebo; RR 0.72, 95% CI 0.60 to 0.84). The review did not state how fractures were diagnosed. The other RCT identified by the review (246 women, 199 men, mean age 71 years, living at home; see comment below) found no significant difference with calcium plus vitamin D reduced overall non-vertebral fractures (11/187 [6%] with calcium plus vitamin D v 26/202 [13%] with placebo; RR 0.46, 95% CI 0.23 to 0.90). Fractures were diagnosed by self report, interview, and validation from case records.19 The subsequent RCT (583 women in
Fracture prevention in postmenopausal women

institutional care) found no significant difference between calcium plus vitamin D3 versus placebo in hip fracture at 2 years (27/393 [6.9%] with calcium plus vitamin D v 21/190 [11.1%] with placebo; RR for placebo v calcium plus vitamin D 1.69, 95% CI 0.96 to 3.00).22

Harms: Vitamin D3 or vitamin D analogue (calcitriol) versus placebo or calcium: The systematic review found that vitamin D or vitamin D analogues versus placebo or calcium increased hypercalcaemia (5 RCTs, 1009 people; 22/498 [4.4%] with vitamin D or vitamin D analogues v 18/511 [3.5%] with placebo or calcium; RR 1.71, 95% CI 1.01 to 2.89).33

Comment: In the RCT comparing calcium versus placebo in subgroups of women with and without existing fractures, randomisation was not stratified according to existing fracture status and there was an unequal number of women taking calcium or placebo in each subgroup.18 In the RCT23 comparing calcitriol versus placebo, identified by the review,19 the rate of vertebral fractures in the calcitriol group did not change over time. The statistical difference in fracture rates observed between the groups may have occurred because people taking calcium had an increase in fracture incidence during the third year of the trial.24 The results of the RCT should be interpreted with caution as they are not by intention to treat, and there was a high withdrawal rate, particularly in the third year. Although some RCTs included both men and women at risk of hip fracture, it is likely that the results are generalisable to postmenopausal women.39,20

OPTION | CALCITONIN

Olivier Bruyere and Jean-Yves Reginster

One large RCT in postmenopausal women found that calcitonin versus placebo significantly reduced new vertebral fractures over 5 years. One systematic review combined evidence from RCTs in men and women who were taking corticosteroids or had osteoporosis or previous fracture. In this heterogeneous population, it found limited evidence that calcitonin non-significantly reduced vertebral or non-vertebral fracture rates compared with placebo, no treatment, calcium, or calcium plus vitamin D.

Benefits: We found one systematic review23 and one subsequent RCT.24 The systematic review (search date 1997, 14 RCTs, 7 RCTs in perimenopausal women with crush fractures or osteoporosis, 7 RCTs in men and women with osteoporosis or taking corticosteroids, 1309 people, exact proportions of women and men not specified; see comment below) compared calcitonin (salcaltonin) versus placebo, no treatment, calcium, or calcium plus vitamin D (see comment below).23 It found that fewer people developed vertebral or non-vertebral fractures with calcitonin versus no calcitonin, but the difference was not significant (vertebral fractures: 166/1190 [14%] people with calcitonin v 96/554 [17%] with no calcitonin; RR 0.80, 95% CI 0.64 to 1.01; non-vertebral fractures: RR 0.48, 95% CI 0.20 to 1.15; no further data provided). The review did not state how fractures were diagnosed.23 One subsequent RCT (1,108 postmenopausal women with osteoporosis receiving calcium
Fracture prevention in postmenopausal women

1000 mg/day and vitamin D 400 IU/day) compared salmon calcitonin nasal spray (100, 200, or 400 IU/day) versus placebo for 5 years.²⁴ It found that calcitonin 200 IU versus placebo significantly reduced the proportion of women with new vertebral fractures over 5 years (51/287 [18%] with calcitonin v 70/270 [26%] with placebo; RR 0.67, 95% CI 0.47 to 0.97). The difference remained significant in women with one to five existing vertebral fractures at baseline (40/207 [19%] v 60/203 [30%]; RR 0.64, 95% CI 0.43 to 0.96). It found no significant difference in vertebral fractures with calcitonin 100 or 400 IU versus placebo.²⁴

Harms: The systematic review gave no information on harms.²³ The subsequent RCT found that nasal spray calcitonin versus placebo increased nasal congestion, nasal discharge, or sneezing (22% with calcitonin v 15% with placebo; P < 0.01; no further data provided).²⁴

Comment: The systematic review commented that its conclusions are limited because many of the RCTs identified did not report the occurrence of fractures, were not double blinded, and only two of the RCTs identified were of over 2 years’ duration.²³ Although the review included some RCTs in both men and women at risk of hip fracture, it is likely that the results are generalisable to postmenopausal women.²³

**OPTION**

**ENVIRONMENTAL MANIPULATION**

John Edwards

We found no RCTs assessing environmental manipulation alone. One RCT in men and women aged over 70 years found no significant difference in fractures over 4 years with health visitor care versus control. Another RCT in people aged over 65 years in institutional care found that a multifactorial intervention (including an environmental manipulation component) versus usual care significantly reduced hip fractures over 34 weeks.

Benefits: We found no systematic review and no RCTs assessing environmental manipulation (see glossary, p 1200) alone. We found one RCT (674 men and women > 70 years) comparing health visitor care (aimed at assessing nutritional deficiencies, reducing smoking and alcohol intake, improving muscle tone and fitness, assessing medical conditions and use of medication, and improving home environment, such as lighting) versus control (not specified).²⁵ It found no significant difference with health visitor versus control in new fractures over 4 years (16/350 [4.5%] with health visitor care v 14/324 [4.3%] with control; RR 1.06, 95% CI 0.52 to 2.13). The RCT did not state how fractures were diagnosed.²⁵ We found a further RCT assessing a multifactorial intervention (including an environmental manipulation component — see hip protector option, p 1196).²⁶

Harms: The RCT examining health visitor care gave no information on harms.²⁵

Comment: Although the RCT examining health visitor care included both men and women at risk of hip fracture, it is likely that the results are generalisable to postmenopausal women.²⁵
Fracture prevention in postmenopausal women

John Edwards

Three RCTs found no significant difference in falls resulting in fracture over 1 year with exercise versus control. One small RCT found no significant difference between a 2 year back strengthening exercise programme versus usual care in vertebral fractures over 10 years. Another RCT in people aged over 65 years in institutional care found that a multifactorial intervention (including exercise) versus usual care significantly reduced hip fractures over 34 weeks.

Benefits: We found one systematic review (search date 2001, 3 RCTs comparing exercise versus control in preventing falls resulting in fracture) and one subsequent RCT. The review did not perform a meta-analysis because of heterogeneity of methods and interventions among trials. The first RCT identified by the review (185 postmenopausal women living in the community who had fractured an upper limb in the previous 2 years) compared advice to walk briskly for up to 40 minutes three times weekly versus advice to carry out upper limb exercises. It found no significant difference in falls resulting in fracture after 1 year (2/81 [2%] with brisk walking v 3/84 [4%] with upper limb exercises; RR 0.69, 95% CI 0.12 to 4.03). The second RCT identified by the review (77 women and 22 men, aged > 65 years, living in the community; see comment below) compared a home based exercise programme (balance and strength exercises plus walking) versus no exercise programme for 14 weeks. It found no significant difference in falls resulting in fracture over 44 weeks (1/45 [2%] with exercise v 0/48 [0%] with no exercise; RR 3.20, 95% CI 0.13 to 76.48). The third RCT (162 women, 78 men, aged > 75 years; see comment below) found no significant difference in falls resulting in fracture over 1 year with a home exercise programme (balance and strength exercises plus walking) versus usual care (2/121 [2%] with home exercise v 7/119 [6%] with usual care; RR 0.28, 95% CI 0.06 to 1.33). The review did not state how fractures were diagnosed in the RCTs. The subsequent RCT (65 postmenopausal women) compared a programme of back muscle strengthening exercises versus usual care for 2 years. It found no significant difference in vertebral fractures at 10 years with strengthening exercises versus usual care (fractures confirmed radiologically; 3/27 [11.1%] with exercise v 7/23 [30.4%] with usual care; P = 0.85). A further RCT examined a multifactorial intervention (including an exercise component) (see hip protector option, p 1196).

Harms: One of the RCTs found that brisk walking versus control significantly increased the number of falls (15.0/100 person years, 95% CI 1.4/ 20.0 person years to 29.0/100 person years — see methods, p 1188). This result should be interpreted with caution as reporting of falls is subject to recall bias.

Comment: Most of the RCTs identified by the review examined falls rather than fractures as the main outcome of interest.
Fracture prevention in postmenopausal women

John Edwards

RCTs in elderly residents of nursing homes (men and women) found that hip protectors versus no hip protectors significantly reduced hip fractures over 9–19 months, but found no significant difference in pelvic fractures. One RCT in people aged over 65 years in institutional care found that a multifactorial intervention (including staff education, environmental manipulation, exercise, walking aids, drug regimen reviews, and hip protectors for those considered at higher risk) versus usual care significantly reduced hip fractures over 34 weeks.

Benefits: Non-vertebral fractures: We found one systematic review\textsuperscript{29} and four subsequent RCTs\textsuperscript{26,30–32} that systematically reviewed (search date 2000) identified six RCTs (3412 people, predominantly women, see comment below) assessing the effects of hip protectors versus no hip protectors on hip fractures.\textsuperscript{29} It could not perform a meta-analysis of all of the RCTs because some of the RCTs used cluster randomisation and others randomised individuals. In the RCTs that randomised individuals, it found that hip protectors versus no hip protectors significantly reduced hip fractures over 9–19 months (3 RCTs, 202 people, 90–100% women in 2 RCTs, proportion of women and men not stated in 1 RCT; 4/111 [4%] v 15/91 [16%]; RR 0.22, 95% CI 0.09 to 0.57). The review did not state how fractures were diagnosed.\textsuperscript{29} The first subsequent RCT (164 elderly women) found that hip protectors versus control significantly reduced hip fractures over about 1 year (1/88 [1%] v 8/76 [10%]; RR 0.11, 95% CI 0.01 to 0.84). The RCT did not state how fractures were diagnosed.\textsuperscript{30} The second subsequent RCT (64 women and 8 men in a nursing home) found no significant difference with hip protectors versus no hip protectors in hip fractures over 1 year (1/36 [3%] v 7/36 [19%]; RR 0.14, 95% CI 0.02 to 1.10), but it may have been too small to exclude a clinically important difference (see comment below). The RCT did not state how hip fractures were diagnosed.\textsuperscript{31} The third subsequent RCT (174 women aged ≥ 75 years) found no significant difference in hip fractures with hip protectors versus no hip protectors at 18 months (8/86 [9.3%] with hip protectors v 7/88 [8.0%] without; RR 1.17, 95% CI 0.44 to 3.08).\textsuperscript{32} It may have lacked power to exclude a clinically important difference. The RCT did not state how hip fractures were diagnosed. The fourth subsequent RCT was a cluster randomised trial (439 men and women resident in institutional care, aged ≥ 65 years, 72% women).\textsuperscript{36} It compared a multifactorial intervention (including staff education, environmental manipulation [see glossary, \(p\) 1200), exercise, walking aids, drug regimen reviews, and hip protectors for those considered at higher risk) versus usual care for 34 weeks. It found that a multifactorial intervention versus usual care significantly reduced hip fractures over 34 weeks (3/188 [1.6%] with active intervention v 12/196 [6.1%] with usual care; RR 0.26, 95% CI 0.07 to 0.91). The RCT did not state how hip fractures were diagnosed. It was not clear which components of the intervention were responsible for reported effects. Pelvic fractures: The systematic review identified three RCTs.\textsuperscript{29} It could not perform a meta-analysis because of methodological differences among the trials. All three RCTs included men and women (see
Fracture prevention in postmenopausal women

The first RCT (1801 people aged > 75 years, about 80% women) identified by the review found no significant difference in pelvic fractures over a mean 11-15 months with hip protectors versus no hip protectors (2/653 [0.3%] with hip protectors v 12/1148 [1%] with no hip protectors; RR 0.29, 95% CI 0.07 to 1.31). The second RCT identified by the review (665 people aged > 69 years living in a nursing home, 70% women) found no significant difference in pelvic fractures over 11 months (0/247 0% with hip protectors v 2/418 [0.5%] with no hip protectors; RR 0.34, 95% CI 0.02 to 7.01). The third RCT identified by the review (64 men and 8 women, aged 71-96 years living in a nursing home) found no significant difference with hip protectors versus no hip protectors in pelvic fractures over 12 months, but it may have been too small to exclude a clinically important difference (0/36 0% with hip protectors v 2/36 [5%] with no hip protectors; RR 0.20, 95% CI 0.01 to 4.03). The review did not state how fractures were diagnosed in the RCTs. One subsequent RCT (174 women aged ≥ 75 years) found no significant difference in pelvic fractures at 18 months with hip protectors versus no hip protectors (2/86 [2.3%] with hip protectors v 2/88 [2.3%] with no hip protectors; RR 1.02, 95% CI 0.15 to 7.10; not stated whether fractures were radiologically confirmed). However, the RCT may have lacked power to exclude a clinically important difference.

Harms: Non-hip or non-pelvic fractures and injuries: One of the RCTs identified by the review (665 people) found that hip protectors versus no hip protectors increased non-hip fractures over 11 months, but the difference was not significant (15/247 [6.1%] with hip protectors v 25/418 [6.0%] with no hip protectors; RR 1.02, 95% CI 0.55 to 1.89). Another small RCT identified by the review found no significant difference in non-hip fractures with hip protectors versus no hip protectors (2/35 [5.7%] with hip protectors v 0/24 [0%] with no hip protectors; RR 3.47, 95% CI 0.17 to 69.27). A third RCT identified by the review (1801 people) also found no significant difference in the proportion of people with lower limb or other non-hip fractures over a mean of 11-15 months with hip protectors versus no hip protectors (23/653 [3.5%] with hip protectors v 59/1148 [5.1%] with no hip protectors; RR 0.69, 95% CI 0.43 to 1.10). The first subsequent RCT found no significant difference in non-hip fractures over a mean 377 days with hip protectors versus no hip protectors (2/88 [2.3%] with hip protectors v 0/76 [0%] with no hip protectors). Another RCT found no significant difference in non-hip and non-pelvic fractures after 18 months (4/86 [4.7%] with hip protectors v 2/88 [4.5%] with no hip protectors; RR 1.02, 95% CI 0.26 to 3.96), but it may have been too small to exclude a clinically important difference.

Falls: One of the RCTs identified by the review found that hip protectors versus no hip protectors increased the proportion of people who fell on the hip, but the difference was not significant (6/101 [7.9%] v 1/40 [2.5%]; RR 3.17, 95% CI 0.41 to 24.5). The first subsequent RCT found no significant difference in the proportion of people sustaining one or more falls over about 1 year (40/88 [45%] v 28/76 [37%]; RR 1.23, 95% CI 0.85 to 1.79). The other five RCTs identified by the review and the second subsequent RCT found a
Fracture prevention in postmenopausal women

similar incidence of falls with hip protectors versus no hip protectors, but gave no information on the proportion of people who fell. These results should be interpreted with caution as reporting of falls is subject to recall bias. Mortality: One RCT identified by the review found no significant difference in mortality over 12 months with hip protectors versus no hip protectors (6/36 [17%] with hip protectors v 8/36 [22%] with no hip protectors; RR 0.75, 95% CI 0.29 to 1.94). The first subsequent RCT also found no significant difference in mortality with hip protectors versus no hip protectors but it may have been too small to exclude a clinically important difference (6/88 [7%] with hip protectors v 8/76 [10%] with no hip protectors; RR 0.85, 95% CI 0.23 to 1.78). Hospital admission: One of the RCTs identified by the review found no significant difference with hip protectors versus no hip protectors in the proportion of people permanently hospitalised over 12 months (10/36 [28%] with hip protectors v 9/36 [25%] with no hip protectors; RR 1.11, 95% CI 0.51 to 2.41). The first subsequent RCT found no significant difference in the proportion of people who were hospitalised for reasons other than fracture over a mean of 377 days, but it may have been too small to exclude a clinically important difference (10/88 [11%] with hip protectors v 9/76 [12%] with no hip protectors; RR 0.96, 95% CI 0.41 to 2.24).

Comment: Much of the evidence is taken from RCTs that included both men and women at risk of hip fracture. However, it is likely that the results are generalisable to postmenopausal women. The results of the second subsequent RCT should be interpreted with caution as 60% of people who entered the trial were lost to follow up. The RCT had protocol violations as three people were allocated to the hip protector group after randomisation when people initially randomised to hip protectors refused to wear them.

OPTION: HORMONE REPLACEMENT THERAPY

RCTs found no consistently significant effect of hormone replacement therapy on vertebral fracture. One systematic review and one subsequent RCT found that hormone replacement therapy versus placebo, no treatment, calcium, or calcium plus vitamin D significantly reduced the proportion of women with non-vertebral fractures. However, another large subsequent RCT found no significant difference in non-vertebral fractures with hormone replacement therapy versus placebo. Another large RCT, comparing oestrogen plus progestin versus placebo in healthy postmenopausal women, was stopped because hormonal treatment increased risks of invasive breast cancer, coronary events, stroke, and pulmonary embolism.

Benefits: Vertebral fractures: We found no systematic review. We found four RCTs. The first RCT (75 postmenopausal women aged 47–75 years with 1 or more vertebral fractures) compared transdermal hormone replacement therapy (HRT) (17β estradiol [estradiol] and oral medroxyprogesterone acetate) versus placebo. It found no significant difference with HRT versus placebo in the proportion of women with at least one vertebral fracture after 12 months, but it may have been too small to exclude a clinically important difference (fractures confirmed radiologically; 7/34 [21%] with HRT
Fracture prevention in postmenopausal women

The second RCT (100 postmenopausal women) compared transdermal oestrogen versus placebo. It found that over a median 9 years (range 6–12 years) oestrogen versus placebo significantly reduced total spine score, an indirect measurement of vertebral fracture rate (P < 0.01), but did not reduce the proportion of women who had vertebral crush fracture (1/57 [2%] with oestrogen v 5/42 [12%] with placebo; RR 0.15, 95% CI 0.02 to 1.22). The third RCT (1006 women 3–24 months past their last menstrual bleeding, aged 45–58 years) compared oral HRT versus placebo. It found no significant difference with HRT versus placebo in the proportion of women who had vertebral fractures at 5 years’ follow up (6/502 [1.2%] with HRT v 4/504 [0.8%] with placebo; RR 2.00, 95% CI 0.62 to 6.40). The fourth RCT (2763 postmenopausal women aged < 80 years) comparing oral HRT versus placebo for a mean 4.1 years found no significant difference in vertebral fractures, but it may have been too small to exclude a clinically important difference (fractures confirmed radiologically; RR 0.7, 95% CI 0.3 to 1.4). Non-vertebral fractures: We found one systematic review and two subsequent RCTs comparing HRT versus placebo, no treatment, calcium, or calcium plus vitamin D. The review (search date 2000, 22 RCTs, 8774 women) found that HRT versus placebo, no treatment, calcium, or calcium plus vitamin D significantly reduced the proportion of women with non-vertebral fractures after 1–10 years’ follow up (258/4929 [5%] v 307/3845 [8%]; RR 0.73, 95% CI 0.56 to 0.94). This reduction remained significant in women taking HRT who had a mean age younger than 60 years (14 RCTs: RR 0.67, 95% CI 0.46 to 0.98; no further data provided). When RCTs in women with a mean age of 60 years or older were analysed, it found no significant difference in non-vertebral fractures with HRT versus placebo (8 RCTs: RR 0.88, 95% CI 0.71 to 1.08; no further data provided). One large subsequent RCT (2763 postmenopausal women aged < 80 years) found no significant difference with HRT versus placebo in hip fractures (fractures confirmed radiologically; 14/1380 [1.0%] with HRT v 13/1383 [0.9%] with placebo; RR 1.1, 95% CI 0.5 to 2.3) or wrist fracture (29/1380 [2.1] with HRT v 29/1383 [2.0] with placebo; RR 1.0, 95% CI 0.6 to 1.7), but it may have been too small to exclude a clinically important difference because the outcomes of interest were rare. The second subsequent RCT (16 608 healthy postmenopausal women aged 50–79 years) compared oestrogen plus progesterin versus placebo. It found that HRT versus placebo significantly reduced hip fractures after a mean 5.2 years’ follow up (fractures confirmed radiologically; 44/8506 [0.52%] with HRT v 62/8102 [0.77%] with placebo; RR of hip fracture 0.66, 95% CI 0.45 to 0.96). Harms: See HRT under secondary prevention of ischaemic cardiac events, p 166. In one of the RCTs identified by the review assessing non-vertebral fractures, 96/464 women (21%) withdrew from the trial, and more women withdrew from the HRT groups versus non-HRT groups (72/232 [31%] women v 24/232 [10%]; RR 3.0, 55% CI 2.0 to 4.6). The most common reasons cited for withdrawal were menstrual disorders and headache. The second subsequent RCT comparing oestrogen plus progesterin versus placebo...
Fracture prevention in postmenopausal women

was stopped after 5.2 years' follow up because of increased risk of invasive breast cancer, coronary events, stroke, and pulmonary embolism among women receiving HRT compared with placebo (invasive breast cancer: 168/8506 [2.0%] with HRT v. 124/8102 [1.5%] with placebo, RR 1.3, 95% CI 1.0 to 1.6; coronary events: 164/8506 [1.9%] with HRT v. 122/8102 [1.5%] with placebo, RR 1.3, 95% CI 1.0 to 1.6; stroke: 127/8506 [1.5%] with HRT v. 85/8102 [1.1%] with placebo; RR 1.4, 95% CI 1.1 to 1.9; pulmonary embolism: 70/8506 [0.8%] with HRT v. 31/8102 [0.4%] with placebo; RR 2.1, 95% CI 1.4 to 3.3).38

Comment: In the second RCT identified by the review37 assessing non-vertebral fractures, the use of multiple treatment groups without the correct statistical analyses limits the validity of the study results.39 In the subsequent large RCTs, prevention of fractures was a secondary outcome, the primary outcome was the prevention of coronary heart disease.39,38 In addition to the RCTs described, we found many observational studies with conflicting results.2,40-48 One non-systematic review of 11 observational studies found a reduced risk of hip fracture in women taking oestrogen compared with non-users.2 A prospective cohort study (9704 women, ≥ 65 years) found a significant reduction in radiologically confirmed hip fractures with oral oestrogen only in women who started HRT within 5 years of menopause and who used it continuously thereafter.49 Other observational studies found similar fracture rates with HRT compared with no HRT.47 We found no observational studies that detected an increased risk of fracture with HRT. Several observational studies found that only 8–20% of women continued HRT for at least 3 years.48,49

GLOSSARY

Environmental manipulation Involves the restructuring of a person’s environment to remove hazards and reduce the risk of falling or a fall resulting in fracture.

Substantive changes

Bisphosphonates One RCT added,8 pamidronate recategorised as likely to be beneficial.

Calcium and vitamin D alone or in combination, vitamin D or vitamin D analogue versus placebo One RCT added;37 conclusions unchanged.

Calcium and vitamin D alone or in combination, calcium plus vitamin D versus placebo One RCT added;22 conclusions unchanged.

Exercise One RCT added;28 conclusions unchanged.

Hip protectors Two RCTs added;26,32 conclusions unchanged.

Hormone replacement therapy One RCT added;38 conclusions unchanged.

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Fracture prevention in postmenopausal women

Fracture prevention in postmenopausal women

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