

# Raloxifene for the treatment of postmenopausal osteoporosis

Raloxifene is used to prevent or treat postmenopausal osteoporosis at a dose of 60 mg daily. Compared with calcium plus vitamin D, raloxifene seems more effective in reducing vertebral fractures in postmenopausal women. Compared with calcium plus vitamin D, raloxifene is not more effective in reducing nonvertebral fractures in postmenopausal women. Raloxifene may be associated with venous thromboembolic events and fatal strokes in postmenopausal women, although the association with fatal strokes was only seen in one study of women at high risk of cardiac events. No excess risk of coronary events is seen with raloxifene. Raloxifene may be less effective than certain bisphosphonates in preventing nonvertebral fractures, although no head-to-head comparisons are available.

**KEYWORDS:** deep venous thromboembolism ■ fracture ■ osteoporosis  
■ postmenopausal ■ raloxifene

**Peter Vestergaard**

Department of Endocrinology  
& Internal Medicine (MEA), Aarhus  
University Hospital THG, Tage Hansens  
Gade 2, DK-8000 Aarhus C, Denmark  
Tel.: +45 89 49 76 52  
Fax: +45 89 49 76 84  
p-vest@post4.tele.dk

Estrogen is a potent inhibitor of osteoclastic bone resorption. After menopause, osteoclastic resorption is accelerated due to the decrease in endogenous estradiol levels. Hormone replacement can prevent bone loss and reduce risk of fractures [1-3]. However, use of estradiol and conjugated estrogens alone (estrogen therapy [ET]) or combined with progestins (estrogen progestin therapy [EPT]) may have serious side effects, including an increased risk of breast cancer [4], myocardial infarction [4], stroke [4,5] and venous thromboembolism [4,6]. For these reasons use of ET or EPT after menopause is discouraged except for short-term treatment (<2 years) of symptoms of menopause [10] (i.e., not for treating or preventing postmenopausal osteoporosis) [7].

Some of these side effects may perhaps be linked to the progestin compound as (e.g., an increased risk of cardiovascular disease (CVD) may be seen with EPT as conjugated estrogen plus progestin) [4], but not with pure conjugated estrogen (ET) [5]. However, ET may only be used in hysterectomized women [5].

The differential effects of estrogens on bone and breast stems from the effects on the estrogen receptor subtypes. The positive effects on bone stems from effects on estrogen receptor- $\beta$ , and the negative effects on breast tissue stems from effects on estrogen receptor- $\alpha$  [8-10]. For these reasons, selective estrogen receptor modulators (SERMs) have been developed. These have agonist effects on bone and antagonistic effects on breast tissue. The SERMs consist of raloxifene, bazedoxifene [11-13], lasofoxifene, arzoxifene [8,14], ospemifene [15] and toremifene [16]. Other drugs,

such as tamoxifen, are also by nature SERMs [17] although tamoxifen is primarily used for the treatment of breast cancer [18,19].

This article will focus on the effects on bone and fracture risk with raloxifene and the side effects on breast tissue, endometrium and the cardiovascular system (risk of stroke, coronary events and deep venous thromboembolism [DVT]).

## Pharmacokinetics, pharmacodynamics & interactions of raloxifene

Raloxifene inhibits osteoclast activity [20], thus decreasing bone resorption and increasing bone mineral density (BMD) [21].

Approximately 60% is absorbed from the gut with a bioavailability of approximately 2% due to first-pass metabolism in the intestinal wall and liver. Raloxifene is metabolized by glucuronidation in the liver to inactive metabolites with a plasma half-life of approximately 27 h. Raloxifene is excreted with the bile and undergoes enterohepatic recirculation. Less than 0.2% of raloxifene is excreted unchanged through the kidneys. The usual dose is 60 mg orally once daily.

Cholestyramine and other resins reduce the absorption of raloxifene, thus inhibiting the enterohepatic recirculation. Raloxifene may reduce the effects of warfarin.

## Comparison of raloxifene & hormone therapy

Few direct comparative studies between raloxifene and ET/EPT exist. Dane *et al.*

Future  
Medicine  part of 

in a short-duration randomized controlled trial (RCT) comparing raloxifene 60 mg per day ( $n = 21$ ) and combined EPT (1-mg estradiol + 0.5 mg norethisterone daily,  $n = 21$ ) reported that for the lumbar spine (LS), the increase in BMD was 2.3% for raloxifene compared with 5.8% for low-dose hormone replacement therapy and corresponding values for total body BMD were 2.9% for raloxifene and 4.6% for EPT after 1 year. The increases were significantly greater in the EPT group than in the raloxifene group [22].

A RCT of 500 postmenopausal women comparing low-dose transdermal estradiol (0.014 mg/day) versus raloxifene 60 mg/day showed that LS bone mineral density increased by 2.4% (95% CI: 1.9–2.9) with microdose estradiol versus 3.0% (95% CI: 2.5–3.5) with raloxifene after 2 years [23]. Raloxifene thus seems less potent than oral estradiol with respect to effects on BMD at doses of 1 mg, whereas lower doses of estradiol may have the same BMD effects as raloxifene.

### Effects of raloxifene

#### ■ Bone mineral density

Raloxifene increases spine and hip BMD compared with placebo [21].

#### ■ Fractures

Regarding fractures as an outcome, one systematic review (search date 2005) [24] and two subsequent RCTs [25–27] comparing raloxifene and placebo exist.

#### Vertebral fractures

A systematic review (five RCTs, 8282 postmenopausal women) reported that both raloxifene 60 mg and raloxifene 120 or 150 mg daily significantly reduced vertebral fractures in postmenopausal women compared with placebo (60 mg: RR: 0.60, 95% CI: 0.49–0.74; 120 or 150 mg: RR: 0.51, 95% CI: 0.41–0.64) [24]. One RCT [28] dominated the results of this systematic review [24] as this RCT contributed 7705 of the 8282 postmenopausal women included. The inclusion criteria for this RCT were women who were at least 2 years postmenopausal, had no severe or long-term disabling conditions but had osteoporosis, defined as low BMD or radiographically apparent vertebral fractures [28]. The risk reduction (RR) rates from this RCT [28] were also similar to those from the systematic review (RR for raloxifene 60 mg/day vs placebo 0.7; 95% CI: 0.5–0.8; RR for raloxifene 120 mg/day vs placebo: 0.6; 95% CI: 0.4–0.7) [28]. A follow-up

study in the same population found that the proportion of women with vertebral fractures remained significantly lower compared with placebo after 4 years (RR for raloxifene 60 mg/day vs placebo: 0.64; 95% CI: 0.53–0.76; RR for raloxifene 120 mg/day vs placebo: 0.57; 95% CI: 0.48–0.69) [29].

A subsequent RCT reported that raloxifene 60 mg daily significantly reduced clinical vertebral fractures compared with placebo (RR: 0.65; 95% CI: 0.47–0.89 with a median duration of follow-up of 5.6 years) [25]. This study included 10,101 postmenopausal women, mean age 67.5 years, with CVD or multiple risk factors for CVD [25]. The exact inclusion criteria were: eligible women were 55 years of age or older, were 1 year or more postmenopausal, and had established coronary heart disease or were at increased risk for coronary heart disease. Participants were required to have a cardiovascular risk score of 4 or more, according to a point system that takes into account the presence of the following: established coronary heart disease (4 points), arterial disease of the leg (4 points), an age of at least 70 years (2 points), diabetes mellitus (3 points), cigarette smoking (1 point), hypertension (1 point) and hyperlipidemia (1 point) [25].

A second subsequent RCT (488 postmenopausal Asian women, mean age 65 years) compared raloxifene 60 or 120 mg daily versus placebo [27]. The specific inclusion criteria were: women who were 2 or more years postmenopausal, no older than 80 years, and who had primary osteoporosis defined as L2–L4 BMD T-score of at least 2.5 standard deviations below the young adult mean. It found that raloxifene significantly reduced clinical vertebral fractures compared with placebo (0 out of 289 [0%] with raloxifene vs 7 out of 199 [4%] with placebo;  $p < 0.01$ ) [27].

In conclusion, raloxifene seems efficient in preventing vertebral fractures in postmenopausal women with osteoporosis.

#### Nonvertebral fractures

A large RCT (7705 postmenopausal women with osteoporosis, aged 31–80 years, mean 67 years) [28] found no significant difference in the proportion of women with nonvertebral fractures between raloxifene 60 or 120 mg daily and placebo after 36 months (8.5% with raloxifene 60 or 120 mg/day vs 9.3% with placebo; RR: 0.9, 95% CI: 0.8–1.1). After 8 years of follow-up, no significant RR was seen with raloxifene (22.8% nonvertebral fractures with raloxifene 60 mg/day vs 22.9% with placebo;

RR: 1.00; 95% CI: 0.82–1.21) [30]. In this extension (CORE), patients could take other bone active drugs, and more patients in the placebo group did so. Also, adherence to drugs was limited.

A second small RCT (143 postmenopausal women, aged  $68 \pm 5$  years) found no significant difference between raloxifene 60 or 120 mg daily and placebo in the proportion of women with any fracture over 1 year (RR: 1.16; 95% CI: 0.77–1.76) [31]. The inclusion criteria for this study were: good health, age 45–75 years, ambulatory, more than 5 years since last menstruation or low serum estradiol and high follicle stimulating hormone.

A secondary analysis of a large RCT (10,101 postmenopausal women, mean age 67.5 years, with CVD or multiple risk factors for CVD) found no significant difference in nonvertebral fractures between raloxifene 60 mg daily and placebo after median duration of follow-up of 5.6 years (428 out of 5044 [8%] with raloxifene vs 438 out of 5057 [9%] with placebo; HR: 0.96; 95% CI: 0.84–1.10) [26].

A further RCT (488 postmenopausal Asian women, mean age 65 years) compared raloxifene 60 or 120 mg daily versus placebo [27]. It found no significant difference in any incident clinical nonvertebral fracture risk between raloxifene and placebo (two out of 289 [0.7%] with raloxifene vs 5 out of 199 [2.5%] with placebo; RR: 0.28; 95% CI: 0.05–1.14) [27].

In conclusion, raloxifene is not efficient for the prevention of nonvertebral fractures such as hip fractures.

#### ■ Raloxifene versus other antiresorptive drugs

Within the group of antiresorptive drugs, several compounds have been shown to be effective in preventing osteoporotic fractures [32]. However, from existing data, the relative efficacy of the individual compounds cannot be determined [32]. A systematic review performed an indirect comparison of alendronate, etidronate, risedronate, calcitonin, raloxifene and estrogen [33]. This indirect comparison used RCTs and performed the comparison using adjustment, although no details of the studies included in the analyses were reported [33]. This review reported that alendronate reduced nonvertebral fracture risk in women compared with calcitonin, estrogen and raloxifene [33]. However, caution is advised in the interpretation of these results due to differences in inclusion criteria, duration of studies and doses used [33].

One RCT compared alendronate and raloxifene, and reported no significant differences in the risk of vertebral fractures between alendronate 70 mg weekly and raloxifene 60 mg daily (RR: 1.08; 95% CI: 0.60–1.95) [34]. However, the study was terminated prematurely after 312 days. Furthermore, no significant difference in risk of nonvertebral fractures could be detected (RR: 0.92; 95% CI: 0.45–1.86) [34]. An observational study showed that raloxifene users experienced more nonvertebral fractures than users of alendronate [35].

The absence of an effect of raloxifene on nonvertebral fractures, and an effect on vertebral fractures is in line with what has been observed for the other SERMs bazedoxifene [11,13] and arzoxifene [36] in RCTs, whereas the SERM lasofoxifene reduced vertebral as well as nonvertebral fracture risk compared with placebo in a RCT [37].

Raloxifene does not seem efficient in preventing nonvertebral fractures, but only vertebral fractures. This is a significant drawback as hip fractures in particular are associated with an increased mortality [38].

#### ■ Combined or sequential therapy with parathyroid hormone or analogs or bisphosphonates

In a direct comparison, 42 postmenopausal women on raloxifene were randomized to raloxifene alone or parathyroid hormone (PTH) plus raloxifene for 12 months [39]. After 1 year of PTH, mean BMD increased by 9.6% in the spine, by 2.7% in total hip, by 3.6% in the trochanter (all significant) and by 1.2% in the femoral neck (not significant). BMD declined by 4.3% in the radius ( $p < 0.05$ ). After PTH withdrawal, BMD declined slightly on continued raloxifene (0.7–2.9% losses; not significant) at all sites, except in the femoral neck, where BMD increased borderline significantly. After 24 months, spine and femoral neck BMD remained significantly higher than at baseline, while radius BMD remained significantly lower (all statistically significant). It was concluded that BMD may increase in the spine and hip, but not the radius with 1 year of PTH treatment in patients on prior raloxifene. Following discontinuation of PTH, raloxifene partially maintains the BMD gains in the spine and hip induced by PTH [39].

In a randomized, double-blind trial comparing teriparatide plus raloxifene ( $n = 69$ ) versus teriparatide plus placebo ( $n = 68$ ) in postmenopausal women with osteoporosis, it was

reported that LS BMD significantly increased by  $5.19 \pm 0.67\%$  from baseline in the teriparatide-alone group [40]. In the combination group, LS ( $6.19 \pm 0.65\%$ ), femoral neck ( $2.23 \pm 0.64\%$ ), and total hip ( $2.31 \pm 0.56\%$ ), BMD significantly increased from baseline to study end point, and the increase in total hip BMD was significantly greater than in the teriparatide-alone group ( $p = 0.04$ ) [40].

The effects of treatment with PTH or analogs may differ in patients previously treated with alendronate or raloxifene. One study evaluated daily subcutaneous injections of 20- $\mu$ g teriparatide were administered for 18 months to 59 postmenopausal women, 60–87 years of age, with BMD T-scores  $\leq -2.0$  who had previously received either alendronate or raloxifene therapy for 18–36 months [41]. During the first 6 months, there were statistically significant group differences in BMD change at the hip (prior alendronate  $-1.8\%$  vs prior raloxifene  $+0.5\%$ ) and at the spine (prior alendronate  $+0.5\%$  vs prior raloxifene  $+5.2\%$ ). After 18 months, mean LS BMD increased by 10.2% in prior raloxifene-treated patients compared with a 4.1% increase in prior alendronate ( $p < 0.05$ ) patients. Furthermore, at 18 months, mean total hip BMD had significantly increased (1.8%,  $p < 0.05$ ) in prior raloxifene-treated patients but was not different from baseline in prior alendronate-treated patients [41].

The effects of raloxifene after PTH was evaluated in one study [42]. After 1 year of teriparatide 20  $\mu$ g/day, postmenopausal women with osteoporosis were randomly assigned to raloxifene 60 mg/day ( $n = 157$ ) or a placebo ( $n = 172$ ) during the next year. This was followed by a year of open-label raloxifene [42]. A decrease in LS BMD in year 2 was seen for both the raloxifene and placebo groups ( $-1.0 \pm 0.3\%$ ,  $p = 0.004$ ; and  $-4.0 \pm 0.3\%$ ,  $p < 0.001$ , respectively). However, the decrease was less with raloxifene than with placebo. Raloxifene treatment reversed the LS BMD decrease during placebo treatment in year 1, resulting in similar decreases 2 years after randomization ( $-2.6 \pm 0.4\%$  [raloxifene–raloxifene] and  $-2.7 \pm 0.4\%$  [placebo–placebo]). At the conclusion of the study, LS and femoral neck BMD were higher than preteriparatide levels. There were no significant differences between the raloxifene–raloxifene and placebo–raloxifene groups (LS:  $6.1 \pm 0.5\%$  vs  $5.1 \pm 0.5\%$ ; femoral neck:  $3.4 \pm 0.6\%$  vs  $3.0 \pm 0.5\%$ ). It was concluded that sequential raloxifene prevented rapid bone loss at the LS and increased femoral neck BMD whether raloxifene was started immediately

or after a 1-year delay following teriparatide treatment [42].

The EUROFORS study corroborated that raloxifene maintained the BMD gains obtained with PTH [43]. Postmenopausal women with osteoporosis and a recent fragility fracture were treated with teriparatide (20  $\mu$ g/day) for 12 months before being randomized to teriparatide ( $n = 305$ ), switch to raloxifene 60 mg/day ( $n = 100$ ), or receive no active treatment during the subsequent year ( $n = 102$ ). Teriparatide treatment for 2 years significantly increased spine BMD by 10.7%. Patients on raloxifene during the second year had no further change in spine BMD compared with the first year (change from baseline, 7.9%). By contrast, patients not receiving active treatment had a BMD decrease of 2.5% in the second year (change from baseline, +3.8%). In the total hip, BMD increases from baseline at 2 years were 2.5% with teriparatide, 2.3% with raloxifene, and 0.5% without active treatment. The changes at the femoral neck were 3.5, 3.1 and 1.3%. The study did not have the power to assess antifracture efficacy. It was concluded that BMD increases during 2 years of teriparatide therapy in women with osteoporosis. Upon discontinuation of teriparatide, raloxifene maintains spine BMD and increases hip BMD [43].

A study on the effects of adding versus switching alendronate or raloxifene to teriparatide concluded that greater bone turnover increases were achieved by switching to teriparatide, whereas greater BMD increases were achieved by adding teriparatide [44].

Regarding fractures, a pooled analysis of the Fracture Prevention Trial and the MORE trial concluded that teriparatide reduced the risk of any new, new adjacent, and new nonadjacent vertebral fractures by 72, 75 and 70%, respectively, compared with the rates in the placebo group [45]. Similarly, compared with the placebo, raloxifene treatment reduced the risk of any new vertebral fracture, new adjacent vertebral fracture, and new nonadjacent vertebral fracture by 54, 54 and 53%, respectively. However, no direct comparison of the two drugs was possible [45].

A study on the combination of raloxifene and alendronate in 331 postmenopausal women reported that, on average, LS BMD increased by 2.1, 4.3, and 5.3% from baseline with raloxifene, alendronate, and raloxifene plus alendronate, respectively [46]. The increase in femoral neck BMD in the raloxifene plus alendronate group (3.7%) was greater than the 2.7 and

1.7% increases in the alendronate ( $p = 0.02$ ) and raloxifene ( $p < 0.001$ ) groups, respectively [46].

The results of this study was supported by a study of 135 postmenopausal women of whom 98 completed this 12-month, randomized, clinical study (35 in the raloxifene group, 31 in the alendronate group and 32 in the combination group) [47].

One study comparing raloxifene with raloxifene plus clodronate showed that 1 year of combined raloxifene plus clodronate therapy induced a higher increase in lumbar BMD than treatment with raloxifene alone [48].

However, none of the combinations of raloxifene and PTH or bisphosphonates are registered indications.

### Effects on other organ systems & side effects

#### ■ Cardiovascular system

A RCT study reported decreased total cholesterol and low-density lipoprotein cholesterol with raloxifene compared with placebo [21]. The inclusion criteria for this study were: women 45–60 years of age, who were within 2–8 years of menopause, who had a lumbar-spine BMD between 2.5 standard deviations below and 2.0 standard deviations above the mean value for normal premenopausal women ( $0.78 \text{ g/cm}^2$  and  $1.27 \text{ g/cm}^2$ , respectively).

#### Effects on parameters of coagulation

One RCT with a duration of 6 months compared conjugated equine estrogen 0.625 mg daily (23 exposed), tamoxifen 20 mg daily (24 exposed), raloxifene 60 mg daily (24 exposed), and placebo (23 control subjects) [49]. The women in this study were included if they had natural spontaneous menopause or surgical ovariectomy from 1 to 20 years prior to recruitment. All women had a normal mammogram within 6 months of study entry. This study reported an increase in certain coagulation factors (factor VII and D-dimer), and a decrease in other (antithrombin, total and free protein S and plasminogen activator inhibitor-1) with estrogen [49]. Tamoxifen-treated patients had a different pattern with an increase in factors VIII, IX, vWf and free protein S, and whereas antithrombin, total protein S, protein C and plasminogen activator inhibitor-1 decreased [49]. The results for raloxifene were similar to those for tamoxifen [49]. However, no increase in factor IX or decrease in protein C was observed [49]. The study concluded that estrogen, tamoxifen and raloxifene affected hemostasis and thus

increased the risk of ischemic lesions by favoring coagulation and impairing anticoagulation [49]. The effects of raloxifene and tamoxifen differed from estrogen, however, the difference between raloxifene and tamoxifen was small [49].

#### Venous thromboembolism

One systematic review from 2007 including nine RCTs with 24,523 postmenopausal women exists [50]. The main outcome was venous thromboembolism in postmenopausal women using raloxifene. This systematic review reported a significantly increased risk of DVT or pulmonary embolism with raloxifene compared with placebo after a median follow-up of 24 months (odds ratio: 1.62; 95% CI: 1.25–2.09) [50]. The systematic review reported a significantly increased risk of both pulmonary embolism and DVT with raloxifene compared with placebo (DVT, odds ratio: 1.54; 95% CI: 1.13–2.11; pulmonary embolism: odds ratio: 1.91; 95% CI: 1.05–3.47) [50].

The RUTH trial enrolled 10,101 postmenopausal women (mean age 67 years) with or at increased coronary heart disease risk; and venous thromboembolic events [51]. It reported an increased risk of venous thromboembolism with raloxifene (incidence rates: 0.39 and 0.27, respectively,  $p = 0.02$ ) [51]. More specifically the RUTH trial reported a significantly higher risk of venous thromboembolism (103 out of 5044 [0.4%] with raloxifene vs 71 out of 5057 [0.3%] with placebo; RR: 1.44, 95% CI: 1.06–1.95) [25].

One further systematic review did not report on adverse effects from the included RCTs [24].

In conclusion, raloxifene increases the risk of DVT in line with what is seen for hormone therapy.

#### Coronary events

The RUTH trial found no significant difference between raloxifene and placebo in cardiovascular outcomes (533 out of 5044 [2%] with raloxifene vs 553 out of 5057 [2%] with placebo; RR: 0.95; 95% CI: 0.84–1.07) [25]. In an extension of a prior RCT (the MORE trial) [52], women on raloxifene 60 or 120 mg daily were assigned to receive raloxifene 60 mg daily (3510 postmenopausal women), and women who had been assigned to receive placebo continued on placebo (1703 women). This study reported no significant difference between raloxifene and placebo in risk of coronary and cerebrovascular events (myocardial infarction, unstable angina, coronary ischemia, stroke or transient ischemic attack) after 4 years (combined coronary and

cerebrovascular events: RR for raloxifene 60 mg/day: 0.86, 95% CI: 0.64–1.15, while RR for raloxifene 120 mg/day vs placebo: 0.98, 95% CI: 0.74–1.30) [52]. A subsequent RCT gave no information on adverse effects [27].

In conclusion, raloxifene does not seem to be associated with a change in the risk of coronary events.

#### Atrial fibrillation

A retrospective observational cohort study (27,257 women with osteoporosis, 21,027 women using alendronate and 6220 using raloxifene; mean follow-up: 304 days) assessed atrial fibrillation with alendronate versus raloxifene [53]. This study was performed in Taiwan as a register study, including data on women whose outpatient visits or hospitalizations involved the main diagnosis of osteoporosis (International Classification of Diseases, Ninth Revision [ICD9-CM] codes: 733.00, 733.01, 733.02, 733.03, and 733.09), for which they were prescribed either alendronate (10 mg once daily or 70 mg once weekly) or raloxifene 60 mg during years 2001 to 2007. This study reported no significant difference between alendronate and raloxifene in atrial fibrillation (HR: 1.07; 95% CI: 0.86–1.33) [53].

#### Stroke

The RUTH trial found a significantly higher risk of fatal strokes (59 out of 5044 [0.22%] with raloxifene vs 39 out of 5057 [0.15%] with placebo; RR: 1.49, 95% CI: 1.00–2.24) [25].

A re-analysis of the RUTH (10,101 postmenopausal women, mean age 67 years with or at increased coronary heart disease risk); and MORE trial, which enrolled 7705 osteoporotic postmenopausal women (mean age 66 years) has also been reported [54]. A Framingham Stroke Risk Score (FSRS) was calculated for all women with no prior cerebrovascular events ( $n = 16,858$ ). The validity of the FSRS was assessed in the placebo groups, and then raloxifene-associated stroke risk was analyzed by FSRS subgroups [54]. For nonfatal strokes, no difference could be shown between raloxifene and placebo in the before-mentioned MORE or RUTH trials [54]. This absence of any difference also held true for all categories of FSRS at baseline of the study [54]. In the RUTH trial, women with low FSRS scores had no increase in fatal strokes in the raloxifene-treated group [54]. However, women with high FSRS ( $\geq 13$ ) had an increased risk of fatal stroke (HR: 1.75; 95% CI: 1.01–3.02) [54]. The MORE trial, by contrast, reported no increase in fatal strokes

with raloxifene [54]. However, most women in the MORE trial had low FSRS (i.e.,  $< 13$ ). The risk of fatal stroke associated with raloxifene may thus be greater in women at high stroke risk.

A secondary end point analysis of the RUTH trial was also reported [51]. The incidences of all strokes was similar in raloxifene- and placebo-treated groups [51]. In women receiving raloxifene the risk of fatal strokes was higher than with placebo [51]. No significant subgroup interactions were found except that there was a higher incidence of stroke associated with raloxifene use among current smokers [51].

A Japanese study reported data from a post-marketing surveillance [55]. This study used the so-called Evista PMS, a postmarketing special investigation on drug use, was initiated in October 2004. Only naive women who started raloxifene treatment for the first time were to be enrolled and were followed for a maximum of 3 years since starting the treatment. Multiple stroke risk factors were present in three of four women with fatal outcome [55]. No increase in stroke was present in raloxifene-treated women, however, the number of observed fatal strokes was small making firm conclusions difficult [55].

An observational study in 4831 women using raloxifene followed for a median of 4.9 years reported that patients who started raloxifene had neither an excess risk of strokes nor of fatal strokes, and no dose–response relationship was present [56]. This study was conducted in Denmark as a register study and covered all patients starting drugs against osteoporosis between 1996 and 2006 and matched controls.

The MORE trial found no significant difference between raloxifene and placebo in the proportion of women suffering coronary and cerebrovascular events (myocardial infarction, unstable angina, coronary ischemia, stroke, or transient ischemic attack) at 4 years (combined coronary and cerebrovascular events: 82 out of 2557 [3.2%] with raloxifene 60 mg/day vs 94 out of 2572 [3.7%] with raloxifene 120 mg/day vs 96 out of 2576 [3.7%] with placebo; RR for raloxifene 60 mg/day vs placebo: 0.86, 95% CI: 0.64–1.15; RR for raloxifene 120 mg/day vs placebo: 0.98, 95% CI: 0.74–1.30) [52].

In conclusion, no excess of stroke may be seen with raloxifene. However, an excess risk of fatal strokes may be seen.

#### Breast cancer

The CORE trial (the extension of the MORE study) found that, compared with placebo,

raloxifene reduced the proportion of women with invasive breast cancer over 8 years by 66% (HR: 0.34; 95% CI: 0.22–0.50) and with estrogen receptor-positive invasive breast cancer over 8 years by 76% (HR: 0.24; 95% CI: 0.15–0.40) [57]. The RUTH trial also reported a decrease in invasive breast cancer with raloxifene compared with placebo (40 out of 5044 [0.15%] with raloxifene vs 70 out of 5057 [0.27%] with placebo; RR: 0.56; 95% CI: 0.38–0.83) [25]. Also the STAR trial (19,747 postmenopausal women with a predicted increased risk of breast cancer randomized to tamoxifen or raloxifene) reported that women who received raloxifene compared with women who received tamoxifen had a lower incidence of uterine cancer (RR: 0.55), endometrial hyperplasia (RR: 0.19), leiomyomas (RR: 0.55), ovarian cysts (RR: 0.60) and endometrial polyps (RR: 0.30), and had fewer invasive procedures performed. Women receiving tamoxifen therapy had more hot flashes, vaginal discharge and vaginal bleeding than women on raloxifene [58].

#### Overall mortality

Using data from the previously mentioned RCTs on raloxifene versus placebo, it was reported that all-cause mortality was 10% lower among women treated with raloxifene 60 mg/day compared with placebo (relative hazard: 0.90; 95% CI: 0.80–1.00) [59]. The lower overall mortality was foremost due to a lower incidence of noncardiovascular deaths, especially a lower rate of noncardiovascular, noncancer-related deaths [59]. However, no population-based data are present to support this.

#### Other

The RCT by Delmas *et al.* reported no difference in uterine endothelium thickness [21].

#### Caveats

Raloxifene is indicated for use in women and not in men. Raloxifene should not be used in patients, who have had prior venous thromboembolism (DVT, pulmonary embolism or retinal vein thrombosis). Raloxifene should not

be used in patients with reduced hepatic function. In patients with pronounced reduction of kidney function, caution should also be shown with use of raloxifene. However, raloxifene has been used in patients with end-stage renal failure on hemodialysis without reports of serious side effects [60]. The study was small (n = 25 on raloxifene and n = 25 on placebo), and larger studies are needed to establish effects and safety in patients with reduced renal function. The study by Hernandez *et al.* showed that raloxifene 60 mg/day increased spine BMD, but not femoral neck BMD after 1 year compared with placebo and that bone turnover markers decreased with raloxifene compared with placebo [60].

Also raloxifene should not be used in women with active endometrial cancer or in women with vaginal bleeding of unknown cause.

#### Future perspective

The main perspective with the SERMs is to develop drugs that are efficient in preventing vertebral as well as nonvertebral fractures. This may be achieved through development of SERMs with more potent action on bone, but perhaps also through combinations of SERMs and other drugs [61]. The main perspective is thus to get maximum efficacy but to maintain a clean safety profile. The optimal SERM would be one that reduces both vertebral and nonvertebral fractures and breast cancer without an increase in venous thromboembolism but without an increase in hot flashes. However, this may be difficult to achieve due to the nature of the SERMs.

#### Financial & competing interests disclosure

*P Vestergaard has received travel grants and fees for speaking from Eli Lilly. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

#### Executive summary

##### Effects

- Compared with calcium plus vitamin D, raloxifene seems more effective in reducing vertebral fractures in postmenopausal women.
- Compared with calcium plus vitamin D, raloxifene is no more effective in reducing nonvertebral fractures in postmenopausal women.

##### Side effects

- Raloxifene may be associated with venous thromboembolic events and fatal strokes in postmenopausal women. However, this was only observed in one study of women at an increased risk of cardiovascular events and not in all studies.

References

- 1 Torgerson D, Bell-Syer S. Hormone replacement therapy and prevention of nonvertebral fractures. A meta-analysis of randomized trials. *JAMA* 285, 2891–2897 (2001).
- 2 Torgerson D, Bell-Syer S. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. *BMC Musculoskeletal Disord.* 2, 7–10 (2001).
- 3 Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr. Rev.* 23, 529–539 (2002).
- 4 Rossouw JE, Anderson GL, Prentice RL *et al.*; Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA* 288, 321–333 (2002).
- 5 Anderson GL, Limacher M, Assaf AR *et al.*; The Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women’s health Initiative randomized controlled trial. *JAMA* 291, 1701–1712 (2004).
- 6 Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 360, 942–944 (2002).
- 7 Vestergaard P, Mosekilde L, Langdahl B. Fracture prevention in postmenopausal women. *Clin. Evid.* 77(10), 1447–1448 (2011).
- 8 Ariazi E, Ariazi J, Cordera F, Jordan V. Estrogen receptors as therapeutic targets in breast cancer. *Curr. Top. Med. Chem.* 6, 181–202 (2006).
- 9 Berrodin T, Chang K, Komm B, Freedman L, Nagpal S. Differential biochemical and cellular actions of premarin estrogens: distinct pharmacology of bazedoxifene-conjugated estrogens combination. *Mol. Endocrinol.* 23, 74–85 (2009).
- 10 Crabtree J, Peano B, Zhang X, Komm B, Winneker R, Harris H. Activity of three selective estrogen receptor modulators on hormone-dependent responses in the mouse uterus and mammary gland. *Mol. Cell Endocrinol.* 287, 40–46 (2008).
- 11 Kanis J, Johansson H, Oden A, McCloskey E. Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. *Bone* 44, 1049–1054 (2009).
- 12 Miller P, Chines A, Christiansen C, Hoek H, Kendler D, Lewiecki E. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. *J. Bone Miner. Res.* 23, 525–535 (2008).
- 13 Silverman S, Christiansen C, Genant H, Vukicevic S, Zanchetta J, de Villiers T. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J. Bone Miner. Res.* 23, 1923–1934 (2008).
- 14 Kendler DL, Palacios S, Cox DA, Stock J, Alam J, Dowsett SA. Arzoxifene versus raloxifene: effect on bone and safety parameters in postmenopausal women with osteoporosis. *Osteoporos. Int.* 23(3), 1091–1101 (2012).
- 15 Gennari L, Merlotti D, Valleggi F, Nuti R. Ospemifene use in postmenopausal women. *Expert Opin. Investig. Drugs* 18, 839–849 (2009).
- 16 Zhou W, Ding Q, Chen L, Liu X, Wang S. Toremifene is an effective and safe alternative to tamoxifen in adjuvant endocrine therapy for breast cancer: results of four randomized trials. *Breast Cancer Res. Treat.* 128, 625–631 (2011).
- 17 Shelly W, Draper M, Krishnan V, Wong M, Jaffe R. Selective estrogen receptor modulators: an update on recent clinical findings. *Obstet. Gynecol. Surv.* 63, 163–181 (2008).
- 18 Baum M, Budzar A, Cuzick J, Forbes J, Houghton J, Klijn J. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 359, 2131–2139 (2002).
- 19 Eastell R, Hannon R, Cuzick J, Dowsett M, Clack G, Adams J. Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J. Bone Miner. Res.* 21, 1215–1223 (2006).
- 20 Bjarnason NH, Sarkar S, Duong T, Mitlak B, Delmas PD, Christiansen C. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. *Osteoporos. Int.* 12, 922–930 (2001).
- 21 Delmas P, Bjarnason N, Mitlak B, Ravoux A, Shah A, Huster W. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N. Engl. J. Med.* 337, 1641–1647 (1997).
- 22 Dane C, Dane B, Cetin A, Erginbas M. Comparison of the effects of raloxifene and low-dose hormone replacement therapy on bone mineral density and bone turnover in the treatment of postmenopausal osteoporosis. *Gynecol. Endocrinol.* 23, 398–403 (2007).
- 23 Schaefer M, Muysers C, Alexandersen P, Christiansen C. Effect of microdose transdermal 17beta-estradiol compared with raloxifene in the prevention of bone loss in healthy postmenopausal women: a 2-year, randomized, double-blind trial. *Menopause* 16, 559–565 (2009).
- 24 Seeman E, Crans G, Diez-Perez A, Pinette K, Delmas P. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporos. Int.* 17, 313–316 (2006).
- 25 Barrett-Connor E, Mosca L, Collins P, Geiger M, Grady D, Kornitzer M. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N. Engl. J. Med.* 355, 125–137 (2006).
- 26 Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw K. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene use for the Heart Trial. *J. Bone Miner. Res.* 23, 112–120 (2008).
- 27 Nakamura T, Liu J, Morii H, Huang Q, Zhu H, Qu Y. Effect of raloxifene on clinical fractures in Asian women with postmenopausal osteoporosis. *J. Bone Miner. Metab.* 24, 414–418 (2006).
- 28 Ettinger B, Black D, Mitlak B, Knickerbocker R, Nickelsen T, Genant H. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 282, 637–645 (1999).
- 29 Delmas P, Ensrud K, Adachi J, Harper K, Sarkar S, Gennari C. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J. Clin. Endocrinol. Metab.* 87, 3609–3617 (2002).
- 30 Siris E, Harris S, Eastell R, Zanchetta J, Goemaere S, Diez-Perez A. Skeletal effects of raloxifene after 8 years: results from the Continuing Outcomes Relevant to Evista (CORE) study. *J. Bone Miner. Res.* 20, 1514–1524 (2005).
- 31 Lufkin E, Whitaker M, Nickelsen T, Argueta R, Caplan R, Knickerbocker R. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J. Bone Miner. Res.* 13, 1747–1754 (1998).



- 32 MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann. Intern. Med.* 148, 197–213 (2008).
- 33 Wehren L, Hosking D, Hochberg M. Putting evidence-based medicine into clinical practice: comparing anti-resorptive agents for the treatment of osteoporosis. *Curr. Med. Res. Opin.* 20, 525–531 (2004).
- 34 Recker RR, Kendler D, Recknor CP, Rooney TW, Lewiecki EM, Utian WH. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone* 40, 843–851 (2007).
- 35 Cadarette SM, Katz JN, Brookhart MA, Stürmer T, Stedman MR, Solomon DH. Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann. Intern. Med.* 148, 637–646 (2008).
- 36 Cummings SR, McClung M, Reginster J, Cox D, Mitlak B, Stock J. Arzoxifene for prevention of fractures and invasive breast cancer in postmenopausal women. *J. Bone Miner. Res.* 26, 397–404 (2011).
- 37 Cummings SR, Ensrud K, Delmas PD, LaCroix AZ, Vukicevic S, Reid DM. Lasofoxifene in postmenopausal women with osteoporosis. *N. Engl. J. Med.* 362, 686–696 (2010).
- 38 Vestergaard P, Rejnmark L, Mosekilde L. Loss of life years after a hip fracture. *Acta Orthop.* 80, 525–530 (2009).
- 39 Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy. *Osteoporos. Int.* 19, 529–535 (2008).
- 40 Deal C, Omizo M, Schwartz EN, Eriksen EF, Cantor P, Wang J. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. *J. Bone Miner. Res.* 20, 1905–1911 (2005).
- 41 Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J. Bone Miner. Res.* 19, 745–751 (2004).
- 42 Adami S, San Martin J, Muñoz-Torres M, Econs MJ, Xie L, Dalsky GP. Effect of raloxifene after recombinant teriparatide [hPTH(1–34)] treatment in postmenopausal women with osteoporosis. *Osteoporos. Int.* 19, 87–94 (2008).
- 43 Eastell R, Nickelsen T, Marin F, Barker C, Hadji P, Farrerons J. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). *J. Bone Miner. Res.* 24, 726–736 (2009).
- 44 Cosman F, Wermers RA, Recknor C, Mauck KF, Xie L, Glass EV. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J. Clin. Endocrinol. Metab.* 94, 3772–3780 (2009).
- 45 Bouxsein ML, Chen P, Glass EV, Kallmes DF, Delmas PD, Mitlak BH. Teriparatide and raloxifene reduce the risk of new adjacent vertebral fractures in postmenopausal women with osteoporosis. Results from two randomized controlled trials. *J. Bone Joint Surg. Am.* 91, 1329–1338 (2009).
- 46 Johnell O, Scheele WH, Lu Y, Reginster J, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J. Clin. Endocrinol. Metab.* 87, 985–992 (2002).
- 47 Sanad Z, Ellakwa H, Desouky B. Comparison of alendronate and raloxifene in postmenopausal women with osteoporosis. *Climacteric* 14, 369–377 (2011).
- 48 D'Amelio P, Muratore M, Tinelli F, Tamone C, Cosentino L, Quarta E. Effect of raloxifene and clodronate on bone density in postmenopausal osteoporotic women. *Int. J. Tissue React.* 25, 73–78 (2003).
- 49 Cosman F, Baz-Hecht M, Cushman M, Vardy MD, Cruz JD, Nieves JW. Short-term effects of estrogen, tamoxifen and raloxifene on hemostasis: a randomized-controlled study and review of the literature. *Thromb. Res.* 116, 1–13 (2005).
- 50 Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. *Thromb. Haemost.* 99, 338–342 (2008).
- 51 Mosca L, Grady D, Barrett-Connor E, Collins P, Wenger N, Abramson BL. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. *Stroke* 40, 147–155 (2009).
- 52 Barrett-Connor E, Grady D, Sashegyi A, Anderson P, Cox D, Hosszowski K. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 287, 847–857 (2002).
- 53 Huang W, Tsai Y, Wen Y, Hsiao F, Kuo KN, Tsai C. Osteoporosis treatment and atrial fibrillation: alendronate versus raloxifene. *Menopause* 17, 57–63 (2010).
- 54 Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D. Raloxifene and risk for stroke based on the Framingham stroke risk score. *Am. J. Med.* 122, 754–761 (2009).
- 55 Urushihara H, Kikuchi N, Yamada M, Yoshiki F, Miyauchi A. Raloxifene and stroke risks in Japanese postmenopausal women with osteoporosis on postmarketing surveillance. *Menopause* 16, 971–977 (2009).
- 56 Vestergaard P, Schwartz K, Pinholt EM, Rejnmark L, Mosekilde L. Stroke in relation to use of raloxifene and other drugs against osteoporosis. *Osteoporos. Int.* 22, 1037–1045 (2011).
- 57 Martino S, Cauley J, Barrett-Connor E, Powles T, Mershon J, Disch D. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J. Natl Cancer Inst.* 96, 1751–1761 (2004).
- 58 Runowicz CD, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Ford LG. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). *Am. J. Obstet. Gynecol.* 205, 535 e1–e5 (2011).
- 59 Grady D, Cauley JA, Stock JL, Cox DA, Mitlak BH, Song J. Effect of raloxifene on all-cause mortality. *Am. J. Med.* 123, 469 e1–e7 (2010).
- 60 Hernandez E, Valera R, Alonzo E, Bajares-Lilue M, Carlini R, Capriles F. Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int.* 63, 2269–2274 (2003).
- 61 Kharode Y, Bodine P, Miller C, Lyttle C, Komm B. The pairing of a selective estrogen receptor modulator, bazedoxifene, with conjugated estrogens as a new paradigm for the treatment of menopausal symptoms and osteoporosis prevention. *Endocrinology* 149, 6084–6091 (2008).

#### ■ Website

- 101 European Medicines Agency public statement on recent publications regarding hormone replacement therapy. [www.emea.eu.int/pdfs/human/press/pus/3306503en.pdf](http://www.emea.eu.int/pdfs/human/press/pus/3306503en.pdf)