The PEARL trial: lasofoxifene and incidence of fractures, breast cancer and cardiovascular events in postmenopausal osteoporotic women

Lasofoxifene is a selective estrogen-receptor modulator with high affinity and selectivity for estrogen receptors, leading to estrogen-agonist effects in some tissues and estrogen-antagonist effects in others. Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) was a global, multicenter, double-blind, placebo-controlled randomized trial which recruited 8556 women between 59–80 years of age with osteoporosis under therapy with lasofoxifene 0.25 mg/d, lasofoxifene 0.5 mg/d, or placebo for 5 years. In postmenopausal women with osteoporosis, lasofoxifene 0.5 mg/day for 5 years reduced the risk of nonvertebral and vertebral fractures, major coronary heart disease, stroke and both total and estrogen receptor-positive invasive breast cancer risk. However, both doses of lasofoxifene increased the risk of venous thromboembolic events.

KEYWORDS: estrogen receptor-positive breast cancer ■ fracture ■ heart disease ■ osteoporosis ■ PEARL trial

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Selective Estrogen-Receptor Modulators (SERMs) are a class of compounds that act on the estrogen receptors (ERs). Lasofoxifene is a nonsteroidal-selective ER modulator that decreases bone reasorption, bone loss and low density lipoprotein (LDL) cholesterol in postmenopausal women [1]. Lasofoxifene appears to represent an advance in the progression of pharmacological agents at our disposal, which can reduce both the risk of fractures in women with osteoporosis and the risk of breast cancer in postmenopausal women [2–4], possibly because it binds with high affinity to both ER-α and ER-β. Previous randomized trials of tamoxifen in postmenopausal women with breast cancer [5] and trials of raloxifene [6,7] and lasofoxifene [1] in healthy postmenopausal women have found favorable changes in lipid levels with treatment. In one study, prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene has been tested. The two doses of lasofoxifene (0.25 mg/day and 1.0 mg/day) and 60 mg/day of raloxifene were equally effective at increasing total hip BMD, which was reflected in a low risk of hip fractures. Compared to raloxifene, lasofoxifene at 2 years produced greater increases of 1.9% (0.4, 3.4) and 2.3% (0.9, 3.6) in lumbar spine BMD, respectively ($p < 0.05$). They significantly reduced the levels of biochemical markers of bone turnover compared with placebo where the effects of lasofoxifene were greater then the response to raloxifene [8]. Also treatment of postmenopausal osteoporotic women with bazedoxifene significantly reduced the risk of vertebral fractures, increased BMD of the hip and spine as well as reduced the bone turnover [9]. Previous randomized trials of tamoxifen [10,11] and raloxifene [12,13] have reported no benefit on the risk of coronary heart disease events and an increased risk of venous thromboembolic events [14]. Multiple studies have shown that tamoxifen reduces the incidence of breast cancer in women at an increased risk of breast cancer [15,16]. Based on these results, tamoxifen and raloxifene were approved by the US FDA for breast cancer risk reduction in pre- and postmenopausal healthy women at high risk for developing breast cancer. The use of effective therapies to prevent breast cancer is low among postmenopausal women with a high breast cancer risk [17,18], perhaps because of the unacceptable side effects or lack of perceived benefit of the therapy on overall health. New agents without serious side effects, which reduce the occurrence of breast cancer and provide additional benefits such as reduction in clinical fractures and other chronic disease, are needed. Lasofoxifene, a potent third-generation SERM, was developed because of its potentially attractive pharmacological profile as an agent for risk reduction of osteoporotic fractures, breast cancer and heart disease in postmenopausal women. The Postmenopausal Evaluation And Risk-Reduction with Lasofoxifene (PEARL) trial was therefore undertaken to evaluate the safety and efficacy of lasofoxifene on the incidence of vertebral fractures at 3 years and nonvertebral fractures and ER-positive breast cancer including ductal carcinoma *in situ* at 5 years in osteoporotic postmenopausal women. Safety end

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points included major coronary events and stroke. In postmenopausal women with osteoporosis, at 5 years with a dose of 0.5 mg per day, lasofoxifene is associated with reduced risk of vertebral and nonvertebral fractures, breast cancer, major coronary events and stroke, with no increase in the risk of endometrial cancer but an increased risk of thromboembolic events and pulmonary embolism, although the increase in absolute risk was very small.

Design of the PEARL study

The PEARL trial (NCT00141323) was a global, multicenter, double-blind, placebo-controlled randomized trial. A total of 8556 women were enrolled at 113 sites in 32 countries. Women between the ages of 59 and 80 years were eligible for the study if they had a BMD T-score of -2.5 or less at the lumbar spine or femoral neck, if they had self-reported good or excellent health, and if they had undergone a mammography within the previous 6 months, with no findings that were suggestive of breast cancer. Subjects received 1 g calcium and 400–800 IU of vitamin D and placebo during a 6–8-week run-in period; women who complied by taking 75% or more of these pills were randomly assigned to receive lasofoxifene, at a dose of either 0.25 mg per day (the lower-dose lasofoxifene group had 2852 patients), or 0.5 mg per day (the higher-dose lasofoxifene group had 2852 patients), or placebo (2852 patients). The trial was planned to continue for 5 years; vertebral fracture was the primary end point for the first 3 years of the trial, and nonvertebral fracture and ER-positive breast cancer were coprimary end points through the 5 years. Secondary end points at 5 years were major coronary events and stroke. Lateral spine radiographs were obtained at 12, 24, 36 and 60 months, and vertebral fractures were diagnosed if two of three criteria were met: an increase of one grade in a 4-point rating of vertebral deformity from normal (0 points) to severe (3 points), a decrease of 20% or more and 4 mm or more in vertebral height, or a qualitative diagnosis of a vertebral fracture [19,20]. All women underwent annual mammographies and clinical breast examinations. The gynecological committee confirmed endometrial cancer or hyperplasia from pathology reports. An expert committee adjudicated coronary events, including deaths from coronary heart disease, nonfatal myocardial infarction, coronary-revascularization procedures, documented new ischemic heart disease and hospitalization for unstable angina. Fasting blood samples were obtained at baseline and 3 years for measurement of levels of LDL cholesterol, high density lipoprotein cholesterol, triglycerides and C-reactive protein.

Results

Major outcomes of lasofoxifene at 5 years of therapy are presented in Figure 1. Lasofoxifene was associated with a reduction in absolute incidence of radiographic vertebral fractures at 3 years of 6.4 (16.6 vs 23.0 fractures per 1000 patient-years) and relative risk reduction of 31% in the lower-dose lasofoxifene group of 9.5 (13.5 vs 23.0 fractures per 1000 patient-years) and relative risk reduction of 42% in the higher-dose lasofoxifene group. Identical reductions (31 and 42%) were observed at 5 years, with reductions in absolute rates of vertebral fractures of 6.4 in the lower-dose lasofoxifene group and 9.3 in the higher-dose lasofoxifene group. As compared with placebo, lasofoxifene at a dose of 0.25 mg per day and at a dose of 0.5 mg per day was associated with a decrease in the absolute incidence of nonvertebral fracture at 5 years, by 2.5 (22.0 vs 24.5 fractures per 1000 patient-years) and 5.9 (18.7 vs 24.5 fractures per 1000 patient-years), respectively, representing 10 and 24% reductions in hazard rates; the reduction was significant for the higher dose but not the lower dose. Over a period of 5 years, bone density improved in the lumbar spine, femoral neck and total hip with both lower (average 2.8%) and higher dose of lasofoxifene (2.9%). At 5 years, 21 women in the placebo group had ER-positive breast cancer, as compared with 11 women in the lower-dose lasofoxifene group and 4 women in the higher-dose lasofoxifene group, representing 48% and 81% decreases in risk, respectively, in the lower-dose and higher-dose lasofoxifene groups. Lasofoxifene was associated with a reduction in the absolute incidence of invasive breast cancer of 1.4 cases per 1000 patient-years and a relative risk reduction of 85% for women receiving 0.5 mg per day; the 21% decrease in the group receiving 0.25 mg per day was not significant. Lasofoxifene, as compared with placebo, was associated with a reduction in the absolute incidence of major coronary heart disease of 1.8 (5.7 vs 7.5 cases per 1000 patient-years; 95% CI: 0.2 to 3.8; hazard ratio, 0.76; 95% CI: 0.56 to 1.03) in the group of patients assigned to the lower dose of lasofoxifene and a reduction of 2.4 (5.1 vs 7.5 cases per 1000 patient-years; 95% CI: 0.50–0.93) in the group assigned to the higher dose; the reduction associated with the higher dose was significant. Lasofoxifene was associated with a reduction in the absolute risk of stroke of 1.5 with 0.25 mg per

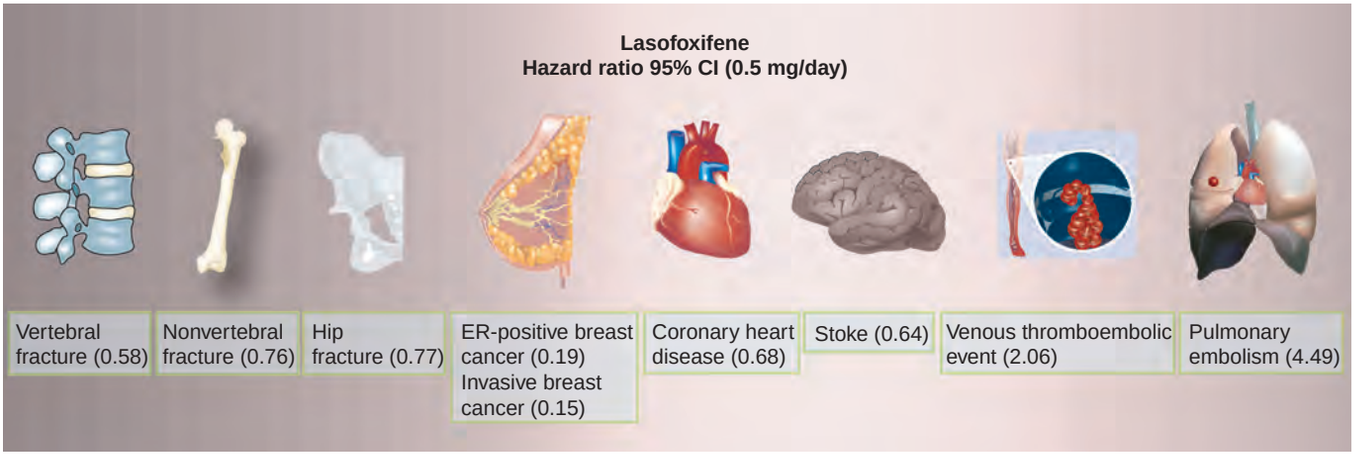

Figure 1. Lasofoxifene clinical outcomes following 5 years of treatment.
ER: Estrogen receptor.

day and a reduction in absolute risk of 1.4 with 0.5 mg per day. In the placebo group, five fatal strokes occurred, as compared with 12 strokes in the lower-dose lasofoxifene group, a difference of 0.5 per 1000 patient-years, and seven strokes in the higher-dose lasofoxifene group, a difference of 0.1 per 1000 patient-years. As compared with placebo, lasofoxifene at a dose of 0.25 mg was associated with an increase in the absolute incidence of a venous thromboembolic event of 2.4, and lasofoxifene at a dose of 0.5 mg was associated with an increase of 1.5. There were two events of pulmonary embolism in the placebo group, 12 events in the lower-dose lasofoxifene group, and nine events in the higher-dose lasofoxifene group.

At 3 years follow-up, as compared with placebo, treatment with lasofoxifene at a dose of 0.25 mg per day was associated with a reduction in the median LDL cholesterol level of 16.2%, and treatment with lasofoxifene at a dose of 0.5 mg per day was associated with reduction in the median LDL cholesterol level of 15.8%. The lower dose of lasofoxifene was associated with an increase in the triglyceride level of 8.0%, and the higher dose was associated with an increase in the triglyceride level of 4.9%. The lower dose of lasofoxifene was associated with a decrease in the median C-reactive protein level of 15.8%, and the higher dose was associated with a decrease in the median C-reactive protein level of 12.5. There was no significant effect on high density lipoprotein cholesterol levels. Endometrial cancers were diagnosed in two women in each lasofoxifene group and three women in the placebo group. Endometrial hyperplasia was confirmed in two women in the higher-dose lasofoxifene group, three women in the lower-dose lasofoxifene group, and no women in the placebo group.

Safety

No significant difference in the rate of death was observed between the higher-dose lasofoxifene group and the placebo group. However, there were 65 deaths in the placebo group (2.3%) (5.1 deaths per 1000 patient-years), 90 deaths in the lower-dose lasofoxifene group (3.2%) (7.0 deaths per 1000 patient-years) ($p = 0.05$), and 73 deaths in the higher-dose lasofoxifene group (2.6%) (5.7 deaths per 1000 patient-years). The maximum number of fatal cancers at individual anatomical sites in the lasofoxifene groups versus the placebo group was three. There were no significant differences between the groups in the rate of all serious adverse events.

Discussion

Treatment of postmenopausal women for 5 years with 0.5 mg lasofoxifene per day, the dose that is intended for clinical use, was associated with a reduction in the risk of vertebral fractures, nonvertebral fractures, ER-positive breast cancer, major coronary events, and stroke and was not associated with an increase in the risk of endometrial hyperplasia. Both doses were associated with an increased risk of a venous thromboembolic event, as seen with estrogen and other selective ER modulators [21–23]. The higher dose of lasofoxifene reduced risk of vertebral fractures by 42% at 3 years which was similar to that observed with raloxifene, estrogen therapy, bisphosphonates and tibolone [24,25]. Also decreased risk of ER-positive breast cancer in association with 0.5 mg lasofoxifene per day is similar to that observed with raloxifene in women with osteoporosis [21]. At 5 years, women assigned to the higher dose of lasofoxifene appeared to have a decreased risk of major coronary heart disease events and stroke.

These findings are in contrast with reported results with tamoxifen, hormone therapy and tibolone [24,26]. It is possible that differences in their effects on the risk of cardiovascular disease reflect differences in their effect on inflammation and C-reactive protein levels [27]. The increased risk of a venous thromboembolic event observed with lasofoxifene is similar to that seen with other ER modulators as well as oral estrogen therapies [21–23]. All selective ER modulators including lasofoxifene, increased hot flushes and leg cramps, but also decreased arthralgia, because arthralgias sometimes occur when estradiol production is blocked. Finally, 5 years of treatment with lasofoxifene did not increase the risk of endometrial cancer or endometrial hyperplasia.

Future perspective

The PEARL study showed that lasofoxifene 0.5 mg/day compared with other currently available SERMS represents an advance in the progression of pharmacological agents for treating osteoporosis, with a favorable benefit-to-risk profile for reduction of nonvertebral fractures, major coronary events, stroke and estrogen-positive breast cancer. That makes it an attractive option particularly for use in postmenopausal women. The inferior fracture efficacy of raloxifene and bazedoxifene compared with bisphosphonates, and the absence of their significant reduction in stroke or coronary heart disease, will position lasofoxifene as a favorable SERM for the older population of postmenopausal women. Future studies on the effect of lasofoxifene on reductions of stroke and major coronary events, which are similar to statins, will position its use, particularly in postmenopausal women with osteoporosis or higher estradiol levels. Also, we will need more complete information about the long-term effects and the biological mechanism of action of lasofoxifene on both beneficial and unfavorable outcomes.

Conclusion

We can conclude that in postmenopausal women with osteoporosis, lasofoxifene at a dose of 0.5 mg per day is associated with a reduced risk of vertebral and nonvertebral fractures, breast cancer, major coronary events and stroke, with no increase in the risk of endometrial cancer but an increased risk of thromboembolic events.

Financial & competing interests disclosure

Dr S Vukicevic is receiving lecture fees from Merck and served as a member of the PEARL Scientific Advisory Committee for Pfizer. The authors have 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 apart from those disclosed.

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Executive summary

Background

- Selective estrogen receptor (ER) modulators decrease bone resorption, bone loss and low-density lipoprotein cholesterol in postmenopausal women.
- Therapy with lasofoxifene is associated with a beneficial impact on the rate of risk reduction of fractures, ER-positive breast cancer and cardiovascular disease.

Methods

- A study to evaluate the effect of lasofoxifene on the risk of fractures, breast cancer and cardiovascular disease (postmenopausal evaluation and risk reduction with lasofoxifene [PEARL]) was an international, randomized, placebo-controlled trial.
- Vertebral fracture was the primary end point for the first 3 years of the trial, and nonvertebral fracture and ER-positive breast cancer were coprimary end points through 5 years.

Results

- Lasofoxifene was associated with a reduction in absolute incidence of radiographic vertebral fractures at 3 years.
- Over a period of 5 years, bone density improved in the lumbar spine, femoral neck and total hip with both a lower (average 2.8%) and higher dose of lasofoxifene (2.9%).
- Lasofoxifene was associated with a reduction in the absolute incidence of invasive breast cancer of 1.4 cases per 1000-patient years and a relative risk reduction of 85% for women receiving 0.5 mg per day; however, the 21% decrease in the group receiving 0.25 mg per day was not significant.
- Lasofoxifene, as compared with placebo, was associated with a reduction in the absolute incidence of major coronary events but an increase in the absolute incidence of a venous thromboembolic event.

Significance

- High-dose lasofoxifene therapy can promote reduction of fractures, invasive breast cancer and major coronary events.
- The relationship of these findings to the impact of duration of therapy longer that 5 years remains to be determined.

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