ORIGINAL ARTICLE

Lasofoxifene in Postmenopausal Women with Osteoporosis

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ABSTRACT

BACKGROUND

The effects of lasofoxifene on the risk of fractures, breast cancer, and cardiovascular disease are uncertain.

METHODS

In this randomized trial, we assigned 8556 women who were between the ages of 59 and 80 years and had a bone mineral density T score of –2.5 or less at the femoral neck or spine to receive once-daily lasofoxifene (at a dose of either 0.25 mg or 0.5 mg) or placebo for 5 years. Primary end points were vertebral fractures, estrogen receptor (ER)–positive breast cancer, and nonvertebral fractures; secondary end points included major coronary heart disease events and stroke.

RESULTS

Lasofoxifene at a dose of 0.5 mg per day, as compared with placebo, was associated with reduced risks of vertebral fracture (13.1 cases vs. 22.4 cases per 1000 person-years; hazard ratio, 0.58; 95% confidence interval [CI], 0.47 to 0.70), nonvertebral fracture (18.7 vs. 24.5 cases per 1000 person-years; hazard ratio, 0.76; 95% CI, 0.64 to 0.91), ER-positive breast cancer (0.3 vs. 1.7 cases per 1000 person-years; hazard ratio, 0.19; 95% CI, 0.07 to 0.56), coronary heart disease events (5.1 vs. 7.5 cases per 1000 person-years; hazard ratio, 0.68; 95% CI, 0.50 to 0.93), and stroke (2.5 vs. 3.9 cases per 1000 person-years; hazard ratio, 0.64; 95% CI, 0.41 to 0.99). Lasofoxifene at a dose of 0.25 mg per day, as compared with placebo, was associated with reduced risks of vertebral fracture (16.0 vs. 22.4 cases per 1000 person-years; hazard ratio, 0.69; 95% CI, 0.57 to 0.83) and stroke (2.4 vs. 3.9 cases per 1000 person-years; hazard ratio, 0.61; 95% CI, 0.39 to 0.96) Both the lower and higher doses, as compared with placebo, were associated with an increase in venous thromboembolic events (3.8 and 2.9 cases vs. 1.4 cases per 1000 person-years; hazard ratios, 2.67 [95% CI, 1.55 to 4.58] and 2.06 [95% CI, 1.17 to 3.60], respectively). Endometrial cancer occurred in three women in the placebo group, two women in the lower-dose lasofoxifene group, and two women in the higher-dose lasofoxifene group. Rates of death per 1000 person-years were 5.1 in the placebo group, 7.0 in the lower-dose lasofoxifene group, and 5.7 in the higher-dose lasofoxifene group.

CONCLUSIONS

In postmenopausal women with osteoporosis, lasofoxifene at a dose of 0.5 mg per day was associated with reduced risks of nonvertebral and vertebral fractures, ER-positive breast cancer, coronary heart disease, and stroke but an increased risk of venous thromboembolic events. (ClinicalTrials.gov number, NCT00141323.)

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Lasofoxifene is a nonsteroidal selective estrogen-receptor modulator that decreases bone resorption, bone loss, and low-density- lipoprotein (LDL) cholesterol in postmenopausal women.[1] We conducted the Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial to determine whether lasofoxifene would reduce the risk of fractures, estrogen receptor (ER)–positive breast cancer, and cardiovascular disease among postmenopausal women with osteoporosis.

METHODS

STUDY DESIGN

The PEARL trial was an international, randomized, placebo-controlled trial. Subjects received 1 g of calcium and 400 to 800 IU of vitamin D and placebo during a 6- to 8-week run-in period; women who received 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) or 0.5 mg per day (the higher-dose lasofoxifene group), or placebo. 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 5 years.

PATIENTS

Women between the ages of 59 and 80 years were eligible for the study if they had a bone mineral density 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 mammography within the previous 6 months, with no findings that were suggestive of breast cancer. Exclusion criteria were diseases affecting bone metabolism; a history of breast cancer, venous thromboembolic disease, or superficial thrombophlebitis within the previous 5 years; a stroke or myocardial infarction in the previous 6 months; treatment with estrogen, raloxifene, or tibolone within the previous 3 months or bisphosphonates, sodium fluoride, or parathyroid hormone for more than 1 month within the previous 2 years; and treatment with oral corticosteroids for 3 months or more within the previous year. Women were excluded if they had a history of endometrial hyperplasia or cancer or if they had had unexplained vaginal bleeding or spotting in the previous year.

All patients were counseled about the effectiveness and availability of alternative treatments for osteoporosis. Patients were excluded if they had a clinical diagnosis of vertebral fracture within the previous 12 months, more than three fractures detected on radiographs of the spine, or a T score of –4.5 or less at the femoral neck or lumbar spine. All patients received 1 g of calcium and 400 to 800 IU of vitamin D daily. Patients underwent annual measurements of bone mineral density at the hip and spine. If bone mineral density was reduced by 7% or more at the hip or by 5% or more at the lumbar spine in any year or by 10% or more at either site during the study, if the T score at either site was less than –4.5, or if there was an osteoporotic fracture, the patient was referred to her physician with this information to consider alternative treatment for osteoporosis. Patients were encouraged to continue taking the study drug if they received a nonhormonal agent such as a bisphosphonate, but the study drug was discontinued if they received hormone therapy or raloxifene.

The patients provided written informed consent, and the trial was approved by institutional review boards at the study sites. Equipoise regarding the use of a placebo was based on the complex and unpredictable effects of selective estrogen-receptor modulators, as well as other agents that stimulate estrogen receptors; on the risks of cardiovascular disease, nonvertebral hip fractures, breast cancer, endometrial cancer, and other types of cancer; and on other important conditions. Establishing these effects and the balance of benefits and risks for these agents has required large placebo-controlled trials.[2-4]

END POINTS

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.[5] Nonvertebral fractures, regardless of the degree of trauma but excluding fractures of the skull, face, fingers, and toes, were confirmed by means of radiographic studies.[6,7]

All women underwent annual mammography and clinical breast examinations. A committee of experts reviewed pathology reports and slides to confirm breast-cancer diagnoses and ER sta-

tus. The gynecology committee confirmed endometrial cancer or hyperplasia from pathology reports.

An expert committee adjudicated coronary heart disease events, including deaths from coronary heart disease, nonfatal myocardial infarction, coronary-revascularization procedures, documented new ischemic heart disease, and hospitalizations for unstable angina. The committee also adjudicated stroke, transient ischemic attacks, venous thromboembolic events (pulmonary emboli, deep-vein thrombosis, or retinal-vein thrombosis), and cause of death.

Fasting blood samples were obtained at baseline and 3 years for measurement of levels of LDL cholesterol, high-density-lipoprotein (HDL) cholesterol, triglycerides, and C-reactive protein.

ADVERSE EVENTS

Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* system. As prospectively planned, all serious adverse events with a P value of less than 0.05 for the comparison between either dose and placebo are reported. Other adverse events are reported if there was a difference of at least 10 cases per 1000 women between either lasofoxifene group and the placebo group and if the P value for the comparisons of either dose with placebo was less than 0.01. All events reported with a P value of less than 0.05 for individual or combined doses are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY OVERSIGHT

A scientific advisory committee, consisting of investigators who were not employed by the study sponsor (Pfizer), oversaw the execution of the protocol and planned the analyses for the manuscript before the unblinding of the study-drug assignments. Editing assistance was provided by an independent medical-writing-services agency paid by Pfizer. The committee members approved the manuscript for publication and vouch for the completeness and accuracy of the data. The sponsor held the data and performed the analyses, and the academic authors received all analyses that they requested. The sponsor designed the protocol and was responsible for the management and quality control of the data. An independent data and safety monitoring committee reviewed unblinded data at least annually.

STATISTICAL ANALYSIS

For the primary analyses, each dose of lasofoxifene was compared with placebo, and the Hochberg procedure was used to control for multiple comparisons.[8] Comparisons of times to events were performed with the use of Cox proportional-hazards models. Statistical significance for time to the first diagnosis of a vertebral fracture was tested by means of the stratified log-rank test. The family-wise type I error was split between the two primary 5-year end points: time to nonvertebral fracture and ER-positive breast cancer. Linear models were used to analyze differences in continuous measurements such as a change in bone mineral density. All analyses were based on the intention-to-treat principle.

For the end point of radiographically defined vertebral fracture at 3 years, 2500 subjects per group provided 90% power to detect a 40% reduction in the risk of vertebral fracture, assuming a 1.5% annual incidence in the placebo group and a two-sided alpha of 0.05. For the year 5 primary end points, 2200 subjects per group provided 98% power to detect a 30% reduction in the risk of nonvertebral fracture, assuming a 3.1% annual incidence in the placebo group and a two-sided alpha of 0.025, and also provided 90% power to detect a 70% reduction in the time to a diagnosis of ER-positive breast cancer, assuming a 0.3% annual incidence in the placebo group and a two-sided alpha of 0.025.

RESULTS

STUDY PARTICIPANTS

A total of 8556 women were enrolled at 113 sites in 32 countries (Table 1). The mean age of the patients was 67 years, and 28% had at least one prevalent baseline radiographically defined vertebral fracture. Assessment of outcomes at 5 years was completed for 6614 randomly assigned patients (77.3%). A total of 1820 patients in the placebo group (63.8%), 1753 patients in the lower-dose lasofoxifene group (61.5%), and 1777 patients in the higher-dose lasofoxifene group (62.3%) received the assigned study drug for 5 years.

FRACTURES AND BONE DENSITY

Lasofoxifene was associated with a reduction in the absolute incidence of radiographic vertebral fractures at 3 years of 6.4 (16.6 vs. 23.0 fractures per 1000 patient-years; 95% confidence interval

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Lasofoxifene		Placebo (N=2852)
	0.25 mg (N=2852)	0.5 mg (N=2852)	
Age — yr	67.5±5.2	67.3±5.2	67.5±5.2
Race — no. (%)†			
White	2111 (74.0)	2108 (73.9)	2118 (74.3)
Asian	530 (18.6)	519 (18.2)	521 (18.3)
Other	211 (7.4)	225 (7.9)	213 (7.5)
Radiographic evidence of vertebral fracture at baseline — no. (%)	804 (28.2)	808 (28.3)	804 (28.2)
Family history of breast cancer — no. (%)	253 (8.9)	246 (8.6)	234 (8.2)
Current smoker — no. (%)	186 (6.5)	179 (6.3)	190 (6.7)
Diabetes — no. (%)	174 (6.1)	154 (5.4)	164 (5.8)
Hypertension — no. (%)	1045 (36.6)	1022 (35.8)	1029 (36.1)
Hysterectomy — no. (%)	554 (19.4)	550 (19.3)	543 (19.0)
Body-mass index	25.2±3.8	25.4±3.7	25.4±3.8
Bone mineral density T score			
Lumbar spine	–3.0±0.7	–3.0±0.7	–3.0±0.7
Femoral neck	–2.3±0.7	–2.2±0.7	–2.2±0.7

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was self-reported.

[CI], 1.9 to 10.8) and a relative risk reduction of 31% (hazard ratio, 0.69; 95% CI, 0.55 to 0.87; P=0.002) in the lower-dose lasofoxifene group and 9.5 (13.5 vs. 23.0 fractures per 1000 patient-years; 95% CI, 5.2 to 13.7) and a relative risk reduction of 42% (hazard ratio, 0.58; 95% CI, 0.45 to 0.73; P<0.001) 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 (16.0 vs. 22.4 per 1000 person-years; 95% CI, 2.9 to 10.0) in the lower-dose lasofoxifene group and 9.3 (13.1 vs. 22.4 per 1000 person-years; 95% CI, 5.9 to 12.7) in the higher-dose lasofoxifene group (Table 2). 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 per 1000 person-years; 95% CI, –1.3 to 6.4) and 5.9 (18.7 vs. 24.5 per 1000 person-years; 95% CI, 2.2 to 9.6), respectively, representing 10% and 24% reductions in hazard rates (Table 2 and Fig. 1); the reduction was significant for the higher dose (P=0.002) but not the lower dose (P=0.19). Over a period of 5 years, bone density improved in the lumbar spine by 3.0% (95% CI, 2.6 to 3.3) in the lower-dose lasofoxifene group and by 3.1% (95% CI, 2.8 to 3.5) in the higher-dose lasofoxifene group, as compared with the placebo group, in the femoral neck by 2.9% (95% CI, 2.5 to 3.2) in the lower-dose lasofoxifene group and by 3.0% (95% CI, 2.7 to 3.4) in the higher-dose lasofoxifene group, and in the total hip by 2.4% (95% CI, 2.1 to 2.7) in the lower-dose lasofoxifene group and 2.7% (95% CI, 2.4 to 3.0) in the higher-dose lasofoxifene group.

BREAST CANCER

At 5 years, 21 women in the placebo group had ER-positive breast cancer (1.7 cases per 1000 person-years), as compared with 11 women in the lower-dose lasofoxifene group (0.9 cases per 1000 person-years) and 4 women in the higher-dose lasofoxifene group (0.3 cases per 1000 person-years), representing 48% (P=0.07) and 81% (P<0.001) decreases in risk, respectively, in the lower-dose and higher-dose lasofoxifene groups (Table 2 and Fig. 2A). Lasofoxifene was associated with a reduction in the absolute incidence of invasive breast cancer of 1.4 cases per 1000-patient years (95% CI, 0.7 to 2.1) and a relative risk re-

Table 2. Major Outcomes at 5 Years.

Outcome	Placebo			Lasofoxifene, 0.25 mg			Hazard Ratio (95% CI)	P Value	Difference in Rates (95% CI)*	Lasofoxifene, 0.5 mg			Hazard Ratio (95% CI)	P Value	Difference in Rates (95% CI)*
	no. of patients	*no. of events*	*no./1000 person-yr*	*no. of patients*	*no. of events*	*no./1000 person-yr*			*no./1000 person-yr*	*no. of patients*	*no. of events*	*no./1000 person-yr*			*no./1000 person-yr*
Nonvertebral fracture	2852	296	24.5	2852	269	22.0	0.90 (0.76 to 1.06)	0.19	–2.5 (–6.4 to 1.3)	2852	230	18.7	0.76 (0.64 to 0.91)	0.002	–5.9 (–9.6 to –2.2)
Vertebral fracture	2744	262	22.4	2734	189	16.0	0.69 (0.57 to 0.83)	<0.001	–6.5 (–10.0 to –2.9)	2748	156	13.1	0.58 (0.47 to 0.70)	<0.001	–9.3 (–12.7 to –5.9)
Hip fracture	2852	35	2.8	2852	31	2.4	0.88 (0.54 to 1.42)	0.60	–0.3 (–1.6 to 0.9)	2852	27	2.1	0.77 (0.46 to 1.27)	0.30	–0.6 (–1.9 to 0.6)
ER-positive breast cancer†	2740	21	1.7	2729	11	0.9	0.52 (0.25 to 1.08)	0.07	–0.8 (–1.7 to 0.1)	2745	4	0.3	0.19 (0.07 to 0.56)	<0.001	–1.4 (–2.2 to –0.6)
Invasive breast cancer	2740	20	1.6	2729	16	1.3	0.79 (0.41 to 1.52)	0.47	–0.3 (–1.2 to 0.6)	2745	3	0.2	0.15 (0.04 to 0.50)	<0.001	–1.4 (–2.1 to –0.7)
Major coronary heart disease event	2852	95	7.5	2852	73	5.7	0.76 (0.56 to 1.03)	0.08	–1.8 (–3.8 to 0.2)	2852	65	5.1	0.68 (0.50 to 0.93)	0.02	–2.4 (–4.4 to –0.5)
Stroke	2852	50	3.9	2852	31	2.4	0.61 (0.39 to 0.96)	0.03	–1.5 (–2.9 to –0.1)	2852	32	2.5	0.64 (0.41 to 0.99)	0.04	–1.4 (–2.8 to 0.0)
Venous thrombo-embolic event	2852	18	1.4	2852	48	3.8	2.67 (1.55 to 4.58)	<0.001	2.4 (1.1 to 3.6)	2852	37	2.9	2.06 (1.17 to 3.61)	0.01	1.5 (0.4 to 2.6)
Pulmonary embolism	2852	2	0.2	2852	12	0.9	5.98 (1.34 to 26.7)	0.008	0.8 (0.2 to 1.4)	2852	9	0.7	4.49 (0.97 to 20.8)	0.03	0.54 (0.0 to 1.1)
All-cause mortality	2852	65	5.1	2852	90	7.0	1.38 (1.00 to 1.89)	0.05	1.9 (0.0 to 3.8)	2852	73	5.7	1.12 (0.80 to 1.56)	0.51	0.6 (–1.2 to 2.4)
Fatal stroke	2852	5	0.4	2852	12	0.9	2.39 (0.84 to 6.78)	0.09	0.5 (–0.1 to 1.2)	2852	7	0.5	1.40 (0.44 to 4.40)	0.57	0.15 (–0.4 to 0.7)

* Differences are for the lasofoxifene group as compared with the placebo group.

† This category includes cases of estrogen-receptor (ER)–positive noninvasive breast cancer (three cases in the placebo group, two cases in the lower-dose lasofoxifene group, and one case in the higher-dose lasofoxifene group).

duction of 85% (hazard ratio, 0.15; 95% CI, 0.04 to 0.50) for women receiving 0.5 mg per day (P<0.001); the 21% decrease in the group receiving 0.25 mg per day (hazard ratio, 0.79; 95% CI, 0.41 to 1.52) was not significant (P=0.47) (Table 2).

CARDIOVASCULAR DISEASE

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, 0.5 to 4.4; hazard ratio, 0.68; 95% CI, 0.50 to 0.93) in the group assigned to the higher dose (Table 2 and Fig. 2B); the reduction associated with the higher dose was significant (P=0.02). Lasofoxifene was associated with a reduction in the absolute risk of stroke of 1.5 (2.4 vs. 3.9 cases per 1000 patient-years; 95% CI, 0.1 to 2.9; hazard ratio, 0.61; 95% CI, 0.39 to 0.96) with 0.25 mg per day and a reduction in absolute risk of 1.4 (2.5 vs. 3.9 cases per 1000 patient-years; 95% CI, 0.0 to 2.8; hazard ratio, 0.64; 95% CI, 0.41 to 0.99) with 0.5 mg per day (Table 2 and Fig. 2C). In the placebo group, 5 fatal strokes occurred (0.4 per 1000 person-years), as compared with 12 strokes (0.9 per 1000 person-years) in the lower-dose lasofoxifene group, a difference of 0.5 per 1000 person-years (95% CI, −0.1 to 1.2; P=0.09), and 7 strokes (0.5 per 1000 person-years) in the higher-dose lasofoxifene group, a difference of 0.1 per 1000 person-years (95% CI, −0.4 to 0.7; P=0.57).

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 (3.8 vs. 1.4 events per 1000 patient-years; 95% CI, 1.1 to 3.6), and lasofoxifene at a dose of 0.5 mg was associated with an increase of 1.5 (2.9 vs. 1.4 events per 1000 patient-years; 95% CI, 0.4 to 2.6) (Table 2 and Fig. 2D). There were 2 events (0.2 per 1000 person-years) of pulmonary embolism in the placebo group, 12 events (0.9 per 1000 person-years) in the lower-dose lasofoxifene group (difference, 0.8 per 1000 person-years; P=0.008), and 9 events (0.7 per 1000 person-years) in the higher-dose lasofoxifene group (difference, 0.5 per 1000 person-years; P=0.03).

At 3 years of 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% (95% CI, 19.7 to 12.7), and treatment with lasofoxifene at a dose of 0.5 mg per day was associated with a reduction in the median LDL cholesterol level of 15.8% (95% CI, 19.5 to 12.0). The lower dose of lasofoxifene was associated with an increase in the triglyceride level of 8.0% (95% CI, 1.5 to 14.6), and the higher dose was associated with an increase in the triglyceride level of 4.9% (95% CI, −2.2 to 11.9%). The lower dose of lasofoxifene was associated with a decrease in the median C-reactive protein level of 15.8% (95% CI, 26.7 to 4.9%; P<0.001), and the higher dose was associated with a decrease in the median C-reactive protein level of 12.5 (95% CI, 25.1 to 0.1, P=0.001). There was no significant effect on HDL cholesterol levels.

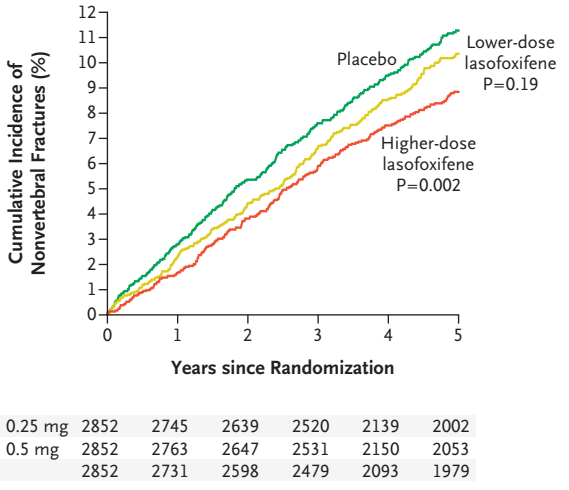

Figure 1. Cumulative Incidence of Nonvertebral Fractures, According to Study Group.

GYNECOLOGIC END POINTS

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 AND ADVERSE EVENTS

No significant difference in the rate of death was observed between the higher-dose lasofoxifene group and the placebo group (Table 2). However, there were 65 deaths in the placebo group (2.3%)

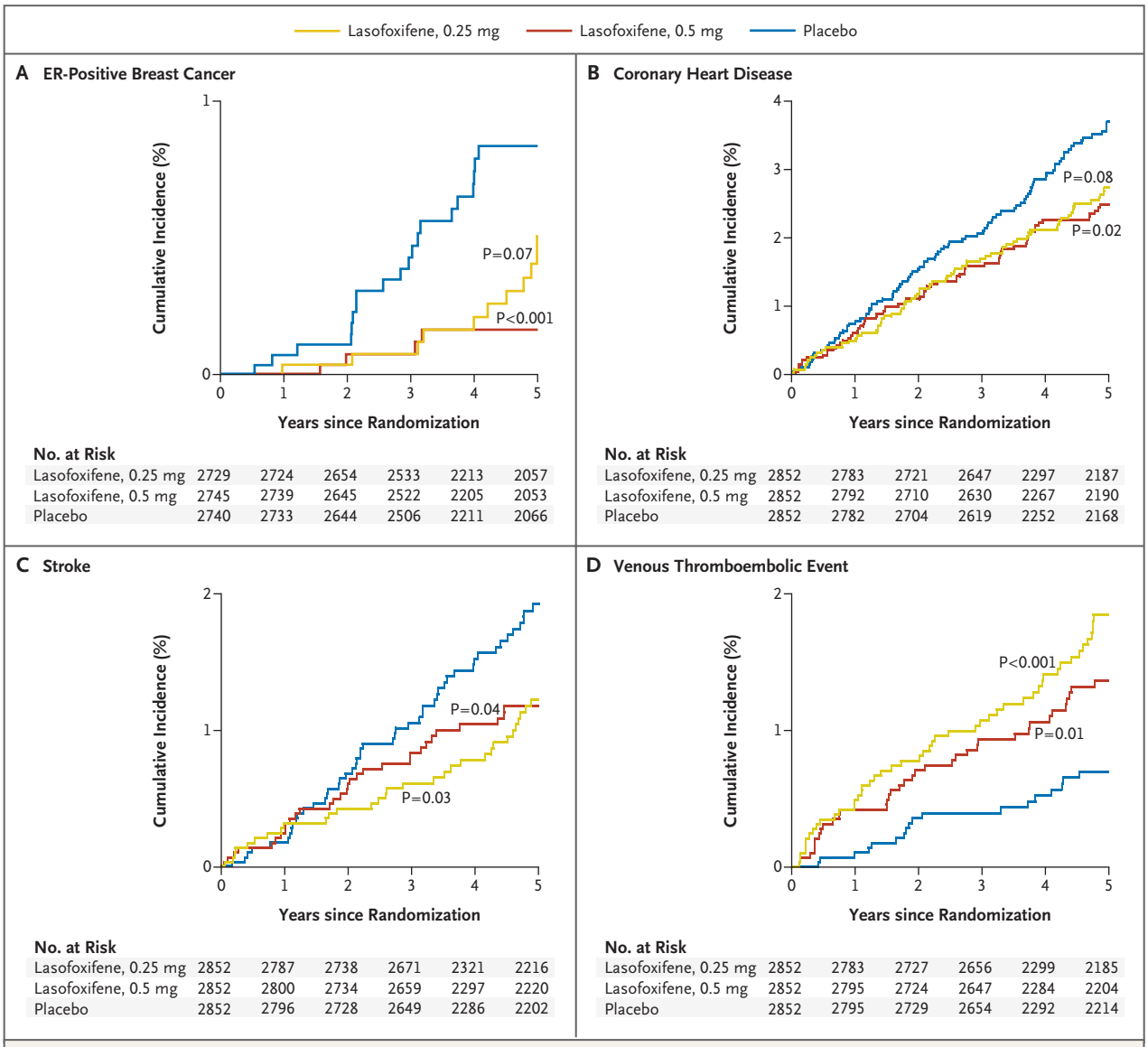

Figure 2. Cumulative Incidence of Events Other than Fracture, According to Study Group.

The cumulative incidence of estrogen-receptor (ER)–positive breast cancer (Panel A), major coronary heart disease (Panel B), stroke (not including transient ischemic attacks) (Panel C), and venous thromboembolic events (Panel D) is shown.

(5.1 deaths per 1000 person-years) and 90 deaths in the lower-dose lasofoxifene group (3.2%) (7.0 deaths per 1000 person-years) (P=0.05). A trend toward more deaths due to cancer in the lower-dose lasofoxifene group (20 cases in the placebo group [0.7%] vs. 34 cases in the lower-dose lasofoxifene group [1.2%]) was close to but not significant (P=0.06); the maximum number of fatal cancers at individual anatomical sites in the lasofoxifene groups versus the placebo group was three. In the higher-dose lasofoxifene group, there were 73 deaths from all causes (2.6%) and 25 deaths due to cancer (0.9%); neither rate was significantly different from that in the placebo group (P>0.50 by the log-rank test). There were 15 cases of primary lung cancer (either squamous-cell carcinoma, adenocarcinoma, small-cell lung cancer, or other types of lung cancer) in the lower-dose lasofoxifene group (0.5%), 13 cases in the higher-dose lasofoxifene group (0.5%), and 4 cases in the placebo group (0.1%).

There were no significant differences between

Table 3. Adverse Events.

Variable	Placebo (N=2852)		Lasofoxifene 0.25 mg (N=2852)		P Value	Lasofoxifene 0.5 mg (N=2852)		P Value
	no. of events	*no./1000 person-yr*	*no. of events*	*no./1000 person-yr*		*no. of events*	*no./1000 person-yr*	
Any serious event*	783	27.4	834	29.2	0.13	784	27.5	0.98
Surgery for prolapse or incontinence	35	2.8	55	4.3	0.04	46	3.6	0.22
All events*	2709	95.0	2725	95.6	0.32	2736	95.6	0.09
Leg cramps†‡	379	29.6	632	49.1	<0.001	720	56.0	<0.001
Hot flushes†	158	12.3	372	28.9	<0.001	365	28.4	<0.001
Uterine polyp†	23	2.2	176	17.1	<0.001	205	19.8	<0.001
Endometrial hypertrophy†	35	3.4	210	20.4	<0.001	167	16.2	0.004
Arthralgia†	867	67.6	738	57.3	0.01	755	58.8	0.004
Vaginal candidiasis†	93	9.0	220	21.4	<0.001	211	20.4	<0.001
Event leading to discontinuation of the study drug*	350	12.3	396	13.9	0.07	367	12.9	0.50
Reason for discontinuation								
Hot flushes*	11	0.4	32	1.1	0.001	30	1.1	0.003
Leg cramps*‡	12	0.4	12	0.4	1.00	26	0.9	0.02

* This category includes patients with one or more events.
† Participants could have more than one adverse event of this type.
‡ This category is based on a composite of *Medical Dictionary for Regulatory Activities* preferred terms. (P values are based on the number of patients with an adverse event corresponding to a preferred term.)

the groups in the rate of all serious adverse events (Table 3). More operations were performed for pelvic prolapse or urinary incontinence in the lower-dose lasofoxifene group than in the placebo group; the difference was not significant for the higher-dose lasofoxifene group. Reports of leg cramps, hot flushes, endometrial hypertrophy, uterine polyps, and vaginal candidiasis were significantly more common in women assigned to lasofoxifene than in those assigned to placebo (Table 3). Arthralgia was less frequent in women receiving lasofoxifene. The rates of permanent discontinuation of the study drug because of adverse events were 12.3% in the placebo group, 13.9% in the lower-dose lasofoxifene group, and 12.9% in the higher-dose lasofoxifene group. Besides venous thromboembolic events, including pulmonary emboli (Table 2), more women receiving either dose of lasofoxifene, as compared with those receiving placebo, discontinued treatment because of hot flushes, and more women receiving 0.5 mg of lasofoxifene per day discontinued the drug because of leg cramps (Table 3, and the Supplementary Appendix).

DISCUSSION

Treatment with 0.5 mg of 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 heart disease events, and stroke and was not associated with an increase in the risk of endometrial cancer or endometrial hyperplasia. Benefits of the lower dose with respect to fracture, breast cancer, and cardiovascular outcomes were less consistent. Both doses were associated with an increased risk of a venous thromboembolic event, as seen with estrogen and other selective ER modulators.[9-11]

The 42% reduction in the risk of vertebral fractures (13.5 vs. 23.0 per 1000 person-years) at 3 years associated with the higher dose of lasofoxifene is similar to that observed with raloxifene, estrogen therapy, oral bisphosphonates, and tibolone.[2,12-17] The decreased risk of nonvertebral fractures is similar to that reported in association with other antiresorptive therapies in women with osteoporosis.[2,12-18] In contrast, raloxifene,

the selective ER modulator currently approved by the Food and Drug Administration for treatment of osteoporosis, does not reduce the risk of nonvertebral fractures. The difference might reflect the fact that lasofoxifene decreases markers of bone turnover and improved spine bone mineral density more than does raloxifene at a dose of 60 mg, although the two agents have similar effects on total-hip bone mineral density.[1]

The decreased risk of ER-positive breast cancer in association with 0.5 mg of lasofoxifene per day is similar to that observed with raloxifene in women with osteoporosis and with tamoxifen and raloxifene in women with a high risk of breast cancer.[10,19,20]

Women assigned to lasofoxifene appeared to have a decreased risk of major coronary heart disease events; the difference was significant for the higher dose. In contrast, estrogen therapy combined with medroxyprogesterone increases the risk of coronary heart disease, and raloxifene has no effect in women at high risk for coronary heart disease.[4,21] Treatment with lasofoxifene at either dose was associated with a decreased risk of stroke. This finding contrasts with the increased risk of stroke reported with tamoxifen, hormone therapy, and tibolone[2,4] and the lack of an effect on the risk of stroke observed with raloxifene in women with osteoporosis.[22] Estrogen, raloxifene, and lasofoxifene all reduce levels of LDL cholesterol.[1,11,23,24] It is possible that differences in their effects on the risk of cardiovascular disease reflect differences in their effect on inflammation: lasofoxifene at a dose of 0.5 mg per day reduced the level of C-reactive protein by 13%, whereas raloxifene has no effect,[25] and estrogen therapy increases C-reactive protein levels.[25]

There were 25 more deaths in the lower-dose lasofoxifene group than in the placebo group ($P=0.05$), but the risk of death was not increased in the higher-dose lasofoxifene group as compared with the placebo group ($P=0.51$). There were more deaths due to stroke and to cancer with 0.25 mg per day, but these differences were not significant, and there were no significant differences for any type or site of cancer. A biologic reason for differences in the rate of death is not clear, and the absence of a significant increase in deaths with the higher dose (0.5 mg per day) suggests that the difference with the dose of 0.25 mg per day might be due to chance. Similarly, there is no clear biologic reason for more cases of several types of primary lung cancer with lasofoxifene than with placebo, and this increase has not been observed with other selective estrogen-receptor modulators.

The increased risk of a venous thromboembolic event observed with lasofoxifene is similar to that seen with raloxifene and tamoxifen, as well as oral estrogen therapies.[9-11] All selective ER modulators studied so far, including lasofoxifene, increase hot flushes and leg cramps.[9,21,26,27] The decrease in arthralgia with lasofoxifene may reflect an estrogenic effect, because arthralgias sometimes occur when estradiol production is blocked by aromatase inhibitors, during menopause, and after discontinuation of estrogen therapy.[4,28] Treatment with tamoxifen and tibolone has also been associated with vaginal infection.[2,29] Five years of treatment with lasofoxifene did not increase the risk of endometrial cancer or endometrial hyperplasia. The greater number of reports of endometrial hypertrophy and polyps may reflect benign endometrial effects that do not confer a predisposition to endometrial cancer or hyperplasia.

This trial has certain limitations. Although the decreases in the risk of breast cancer, coronary heart disease events, and stroke were significant, the numbers of these events were small. The trial included women with osteoporosis; the effect of treatment on the risk of fractures might differ in women with higher bone density. The trial tested 5 years of therapy. Some of the effects of lasofoxifene may vary if longer-term treatment occurs. Follow-up after 5 to 8 years of treatment with tamoxifen has shown that the reduction in the risk of breast cancer or mortality associated with breast cancer persists for at least 10 years; however, it is not known whether this is also true of treatment with raloxifene or lasofoxifene.[30-32]

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

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APPENDIX

The following persons participated in the study: **Scientific Advisory Committee** — S.R. Cummings (chair), P. Delmas, R. Eastell (cochair), K. Ensrud, A. LaCroix, D. Reid, U. Sriram, S. Vukicevic, J. Zanchetta. **Breast Cancer End-Point Classification Committee** — T. Powles, C. Allred, P. Goss, K. Osborne. **Gynecologic End-Point Classification Committee** — T. Colgan, S.R. Goldstein, P. Neven, C.D. Runowicz. **Cardiovascular End-Point Classification Committee** — L. Cohen, U. Sechtem, F. Welty. **Data and Safety Monitoring Committee** — S.R. Johnson, G. Russell, F. Cosman, P. Barter, N.M. Laird. **Investigators** — *Argentina:* A.A. Gardiol, J. Zanchetta, O.D. Messina; *Australia:* E. Seeman, G. Nicholson, M. Hooper, J.J. Graham, J. Eden, B.G.A. Stuckey; *Belgium:* P. Geusens, S. Boonen; *Brazil:* N.R. De Melo, C.A.F. Zerbini; *Canada:* C.-K. Yuen, J. Brown, L.G. Ste.-Marie, J. Adachi, D.A. Hanley, R.G. Josse, D. Kendler, W.P. Olszynski; *Costa Rica:* R. Castro; *Croatia:* D. Krpan, Z. Giljevic, F. Skreb; *Denmark:* L. Hyldstrup, B.L. Langdahl; *Egypt:* A. Rashed; *Estonia:* K. Maasalu, L. Tammemae, K.-L. Piirisild; *Finland:* J. Heikkinen, M. Kormano, M.J. Valimaki; *France:* C.C. Roux, P.D. Delmas; *Germany:* M. Hartard, M. Doren; *China:* E. Lau; *Hungary:* A. Balogh, K. Horvath, Z. Tulassay; *India:* P.M. Kanakatte, B. Srinivasan, R.N. Mehrotra, R. Patni, P.S. Menon, M. Thomas, M.S. Seshadri, A.C. Ammini; *Ireland:* M. O'Brien; *Italy:* M.L. Brandi, S. Adami; *Japan:* A. Itabashi, S. Okamoto, N. Fujita, A. Sawamoto, R. Omata; *Korea:* I.-K. Han; *Lithuania:* V. Alekna, G. Kazanavicius, R. Jurgutis; *Mexico:* I. Balderas, J. Santos, R. Correa-Rotter; *Norway:* J.I. Halse, K. Hoye, E.S. Ofjord; *Poland:* A. Sawicki, E. Marcinowska-Suchowierska, E. Czerwinski; *Romania:* I. Zosin, E. Zbranca, C. Codreanu; *Russia:* A.M. Gzgzyan, L.I. Benevolenskaya, I.I. Dedov, R. Oganov, V. Smetnik; *South Africa:* P.J. Jordaan, T.J. De Villiers, S. Lipschitz, G. Ellis; *Spain:* J. Calaf, F. Hawkins; *Sweden:* D. Mellstrom; *Turkey:* A. Kucu kdeveci, Y. Kirazli; *United Kingdom:* R. Keen, D.M. Reid, N. Savani; *United States:* A.H. Moffett, Jr., J.C. Silverfield, M.A. Bolognese, J.M. McKenney, J. Rosenstock, M.W. Greenwald, M. Lewiecki, S.S. Miller, S.N. Lederman, C.H. Chesnut III, J.C. Gallagher, T.N. Hangartner, K.C. Johnson, K. Ensrud, J.A. Cauley, A. LaCroix, C.E. Lewis, S.B. Broy, L. Sherman, E.L. Barrett-Connor, R.B. Wallace, E.S. Orwoll.

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