BJOG: an International Journal of Obstetrics and Gynaecology
February 2003, Vol. 110, pp. 157–167

A multicentre randomised trial to compare uterine safety of raloxifene with a continuous combined hormone replacement therapy containing oestradiol and norethisterone acetate

Patrick Neven*, Tore Lunde, Pierluigi Benedetti-Panici, Aila Tiitinen, Bogdan Marinescu, Tobie de Villiers, Tim Hillard, Antonio Cano, Eitan Peer, Deborah Quail, Thomas Nickelsen

Participants in the Euralox 1 Study Group are listed on pages 165–166

Objective To compare the uterine effects of 60 mg of raloxifene with a continuous combined hormone replacement therapy, a preparation of 2 mg 17β-oestradiol (E_2) and 1 mg norethisterone acetate for a duration of 12 months.

Design A randomised, double-blind trial.

Setting Multicentre: Europe, Israel, South Africa.

Population Asymptomatic postmenopausal women with risk factors for osteoporosis or cardiovascular disease who had an endometrial thickness of less than 5 mm. One thousand and eight women were randomised for the six month core; of these 420 were invited to continue into a six month extension period.

Methods Randomisation to either raloxifene or continuous combined hormone replacement therapy. Patients, recruiters and assessors were blinded to the treatment used.

Main outcome measures The frequency of vaginal spotting/bleeding as recorded in a diary, endometrial thickness and uterine volume as measured by transvaginal ultrasonography at baseline and after 6 and 12 months.

Results After six months of therapy with raloxifene, the rate of women on raloxifene reporting vaginal bleeding and spotting (6.8%) was similar to the rate in the lead-in phase (8.3%) but increased from 7.0% to 55.1% in the continuous combined hormone replacement therapy group. Raloxifene treatment was not associated with a significant change from baseline to endpoint in mean endometrial thickness ($P = 0.11$), whereas continuous combined hormone replacement therapy treatment was associated with an increase in this value of mean (SD) of 1.2 (2.2) mm ($P < 0.001$). Compared with raloxifene, mean endometrial thickness for women on continuous combined hormone replacement therapy was significantly increased at endpoint [4.6 (2.1) mm *vs* 3.5 (1.7) mm; change from baseline $P < 0.001$]. In the raloxifene group, there was a trend towards a decrease from baseline in uterine volume [from 31.4 (20.3) to 30.3 (16.2) mm; $P = 0.37$]; in the continuous combined hormone replacement therapy group, there was a significant increase in uterine volume [from 31.3 (16.3) to 54.0 (36.1) mm; $P < 0.001$], and the difference in the effect of both compounds on change in uterine volume at endpoint reached statistical significance ($P < 0.001$). Statistically significant differences between the treatment groups were sustained for all parameters during the extension period. Early discontinuation rates, both overall and due to adverse events, were significantly lower ($P < 0.001$) in the raloxifene group after 6 and 12 months.

Conclusion Compared with continuous combined hormone replacement therapy, 6 and 12 months of raloxifene treatment do not lead to vaginal bleeding/spotting, are not associated with increased endometrial thickness or uterine volume and result in a significantly lower rate of early treatment discontinuations in asymptomatic women receiving treatment to prevent long term postmenopausal health risks.

INTRODUCTION

Asymptomatic postmenopausal women are at risk of developing osteoporosis and cardiovascular disease, both of which are major causes of morbidity and mortality in the elderly. Hormonal replacement therapy is widely prescribed for preventing both disorders but compliance is low mainly because of breast pain, fear of increased breast cancer incidence, resumption of menses or irregular vaginal spotting and bleeding[1]. The current hormonal replacement therapy controversy around cardiovascular efficacy has even more decreased compliance[2]. Continuous combined hormonal replacement therapy has been reported to cause

* **Correspondence**: Dr P. Neven, Department of Gynecological Oncology, UZ-Gasthuisberg, Herestraat 49, B-3000 Louvain, Belgium.

PII: S1470-0328(02)02952-X

less spotting and bleeding than cyclic hormonal replacement therapy. Clinical trial data demonstrate, however, that vaginal spotting and bleeding occurs in up to 40% of continuous combined hormone replacement therapy users for as long as three years after the initiation of therapy[3]. The possibly increased risk of developing breast cancer[2], although small, remains a major concern with any form of hormonal replacement therapy as long as long term randomised controlled trials are not available for formulations other than those used in the Women's Health Initiative study[2,4].

Selective oestrogen receptor modulators, such as tamoxifen and raloxifene, prevent bone loss and lower cholesterol levels in postmenopausal women; in addition, raloxifene significantly reduces the risk of osteoporotic vertebral fractures[5,6]. Therefore, selective oestrogen receptor modulators offer a valuable alternative to hormonal replacement therapy in the prevention and treatment of postmenopausal osteoporosis especially because they are also promising as being protective against hormone-dependent breast cancer[7–9]. Tamoxifen, however, shows stimulatory effects on the endometrium and long term intake may lead to endometrial cancer[10]. Preclinical and clinical uterine data as a primary or secondary endpoint indicate that raloxifene, unlike hormonal replacement therapy or tamoxifen, does not stimulate the uterus[11–16].

Euralox 1 is the first prospective, double-blind trial designed to compare the uterine effects of raloxifene in postmenopausal women with those of a typically European continuous combined hormone replacement therapy regimen. This specific objective was chosen because, for many, the latter therapy is the standard of care due to its presumed bleeding-free feature. Commonly prescribed formulations of continuous combined hormone replacement therapy vary widely with respect to the composition and dosages of their respective oestroprogestin components. However, the endometrial and uterine effects of many currently available European continuous combined hormone replacement therapy regimens, containing oestradiol (E_2) and nortestosterone derivatives, have not been properly investigated in large controlled randomised trials. Most of the observational and prospective randomised trials comparing uterine safety with continuous combined hormone replacement therapy use combinations with conjugated equine oestrogens and medroxyprogesterone acetate.

Our results include a follow up period of six months in all patients and an additional six month extension period in a representative subset consisting of approximately 40% of the total study population. They allow a direct comparison of the following primary endpoints with raloxifene with those of a standard continuous combined hormone replacement therapy: frequency of uterine bleeding and spotting, endometrial thickness and uterine volume.

METHODS

This phase 3, multicentre, parallel, randomised, double-blind study was conducted between December 1997 and February 2000 in 129 gynaecological clinics throughout Europe, Israel and South Africa. Postmenopausal women whose risk–benefit assessment suggested a benefit from the long term use of continuous combined hormone replacement therapy and raloxifene were recruited through November 1998. All eligible women were randomly assigned to one of the two treatment groups, namely, raloxifene HCl 60 mg (Evista) or a continuous combined hormone replacement therapy preparation of 2 mg 17β-E_2 and 1 mg NETA (Kliogest/Kliofem) per day. The study consisted of a screening period of four to seven weeks in which the menstrual log and single-blinded lead-in placebo medication were initiated, a double-blind treatment period of six months duration (core phase) and an optional study extension to one year in pre-defined centres from 6 of the 19 participating countries.

The study protocol and informed consent form complied with the guidelines of the Declaration of Helsinki and were approved by local ethical review boards.

Eligible patients were healthy and ambulatory women who were in their natural menopause for at least two years, below 66 years of age and had no known history of oestrogen-dependent cancer, hysterectomy or thromboembolic disorders. Subjects had to have an expected benefit from either treatment in the investigator's opinion. Exclusion criteria included history of other cancer in the past five years, severe subjective postmenopausal symptoms requiring hormone replacement therapy in the investigator's opinion and regular (>1 cycle) use of hormone replacement therapy/oestrogen replacement therapy in the past six months. Eligible subjects were enrolled in the screening period (visit 1) of the study.

Screening involved a gynaecological examination with Papanicolaou's test, transvaginal ultrasonography, blood draw and mammography. All transvaginal ultrasonographies were tape recorded. The uterus was examined in three dimensions and the endometrial thickness of the long and short axis projection from one endometrial/myometrial interface (double layer) to the opposite interface was recorded. All transvaginal ultrasonography tapes were reassessed by a central reader (PN) who was blinded with respect to the treatment code. General instructions for transvaginal ultrasonography, tape recording, saline infusion sonography and hysteroscopy were provided in a standardised way. Still images were analysed from the tape recordings. A minimum of quality of the videotapes was required, otherwise a new tape was requested within two weeks by the central reader. The efficacy analysis of the study was performed based on the results from the central reading. According to local medical practice and patient willingness, patients who were eligible for further screening did (group A) or did not (group B) undergo a blind

endometrial Pipelle biopsy at visit 1. Women with any clinically significant endometrial (endometrial thickness >5 mm or focal abnormalities) or ovarian pathology as determined by central reading of transvaginal ultrasonography or endometrial biopsy at baseline were excluded. The screening period between visit 1 and randomisation (visit 2) was to last a minimum of 28 days and no longer than 50 days. Between these visits, baseline bleeding data were recorded in the menstrual log. To control for possible placebo effects on the bleeding pattern and on several of the secondary endpoints not presented in this paper (such as compliance with study drug and parameters of subjective wellbeing), all subjects received two placebos per day in a single-blind manner: one placebo tablet identical to tablets of raloxifene HCl 60 mg and one placebo capsule identical in appearance to encapsulated continuous combined hormone replacement therapy.

At randomisation, a double-dummy kit containing either raloxifene 60 mg or continuous combined hormone replacement therapy was dispensed. Double-blinded study medication was provided to the participating centres in labelled containers, and randomisation was performed by assigning numbered medication kits in sequence, beginning with the lowest number available. The random allocation sequence of medication kits was created by the sponsor using a computer programme and a block size of 4.

All women presented after three months for visit 3, but no routine uterine procedures were performed. The frequency of uterine bleeding and vaginal spotting was recorded in a diary that the participants were instructed to keep throughout the study. For each case of vaginal spotting/bleeding, patients in group B were subjected to uterine testing in accordance with a protocol-specific gynaecological surveillance algorithm: saline infusion sonography or hysteroscopy/biopsy were performed when transvaginal ultrasonography revealed an endometrial thickness >5 mm. If the endometrium as measured with saline infusion sonography was uniformly thin (<3 mm), there was no further testing, whereas a Pipelle biopsy was advised in case of a uniformly thickened endometrium. Hysteroscopy or dilation and curettage was required in case of asymmetrical thickening. In case of disagreement on endometrial thickness between the investigator and the central reader, the central reader makes a recommendation on further diagnostic procedures to the investigator to be performed within one month. After six months, at visit 4, all women had a transvaginal ultrasonography performed with an endometrial Pipelle biopsy for those women participating in group A. In case of repeated bleeding/spotting for more than three months or an endometrial thickness >5 mm, the uterine algorithm was followed as described for visit 3.

Women from predetermined investigative centres in 6 of the 19 participating countries were chosen to continue a six month extension period in which they continued double-blind medication in the same treatment arm as before. The final visit for this subpopulation (visit 5) occurred 12 months after randomisation or at the time of early discontinuation of study medication.

The main research hypothesis of the trial was that treatment with raloxifene, in contrast to continuous combined hormone replacement therapy, would not be associated with any sign of endometrial proliferation. Bleeding/spotting rates and the changes in endometrial thickness and uterine volume were the primary endpoints of the study. Of these, the change in endometrial thickness was expected to show the subtlest differences and therefore determined the sample size. The planned sample size was calculated to be sufficient to allow the detection of a 0.40 mm difference in endometrial thickness between the two treatment arms with 80% power, assuming a standard deviation of 2.45 mm and a 20% dropout rate.

A number of secondary outcome measures were also defined and will be reported elsewhere. All data were entered into a computer database for analysis by the Biostatistics Section of Eli Lilly. Patients, investigators, all other site personnel and the central reader as well as all other individuals involved in the trial were kept blinded with respect to the treatment until the database was locked.

All patients who were randomised and who had a baseline (pre-randomisation) and at least one postbaseline assessment were included in the analyses of change from baseline described in the group to which they were assigned (intention-to-treat). For patients who discontinued the study early, their last values were carried forward to the six month endpoint (12 month endpoint for extension patients) in the analyses. Analyses of bleeding and spotting rates included all patients who kept data in the diary on bleeding/spotting for at least one four week period postbaseline. Changes between baseline and endpoint in endometrial thickness and uterine volume were analysed using analysis of variance. Data from investigators within a country were pooled and terms for treatment and country were included in the model. The statistical significance of the interaction between treatment and country was investigated and found to be non-significant ($P > 0.10$) in all cases. Within-group changes were compared with zero using paired t tests for normally distributed data (endometrial thickness and uterine volume); otherwise the Wilcoxon signed rank procedure was used (days of bleeding or spotting per month). The proportions of patients with bleeding and spotting were compared between treatment groups using Cochran–Mantel–Haenszel tests controlling for country. Where these proportions were compared across subgroups within each treatment group, either Fisher's exact tests (smokers *vs* non-smokers) or Mantel–Haenszel χ^2 tests (across three pre-defined age groups and three pre-defined years postmenopause groups) were used. All statistical tests were two-sided. Tests of the statistical significance of the interactions between treatment and each of the subgroups were derived using logistic regression models of the log odds of bleeding with factors treatment, subgroup and the interaction.

RESULTS

Figure 1 gives the number of women screened, randomised, withdrawn and analysed in the core and extension phases of the study. A total of 1236 women were recruited to visit 1 during the enrolment time; 1008 and 420 women were found eligible for randomisation to raloxifene or continuous combined hormone replacement therapy for 6 and 12 months, respectively. There were no major differences in baseline characteristics between treatment groups for women in the core (Table 1) and extension phases of the study (data not shown). The core and extension phases of the study were completed by 838 and 314 women, respectively. Bleeding diaries were completed for at least one postbaseline four week period in the core and extension phases of the study by 982 and 410 patients, respectively. These figures for the core and extension phases of the study were 840 and 365 for endometrial thickness, respectively, and 829 and 362 for uterine volume measurements, respectively; we refer to Fig. 1 for all other data per treatment group.

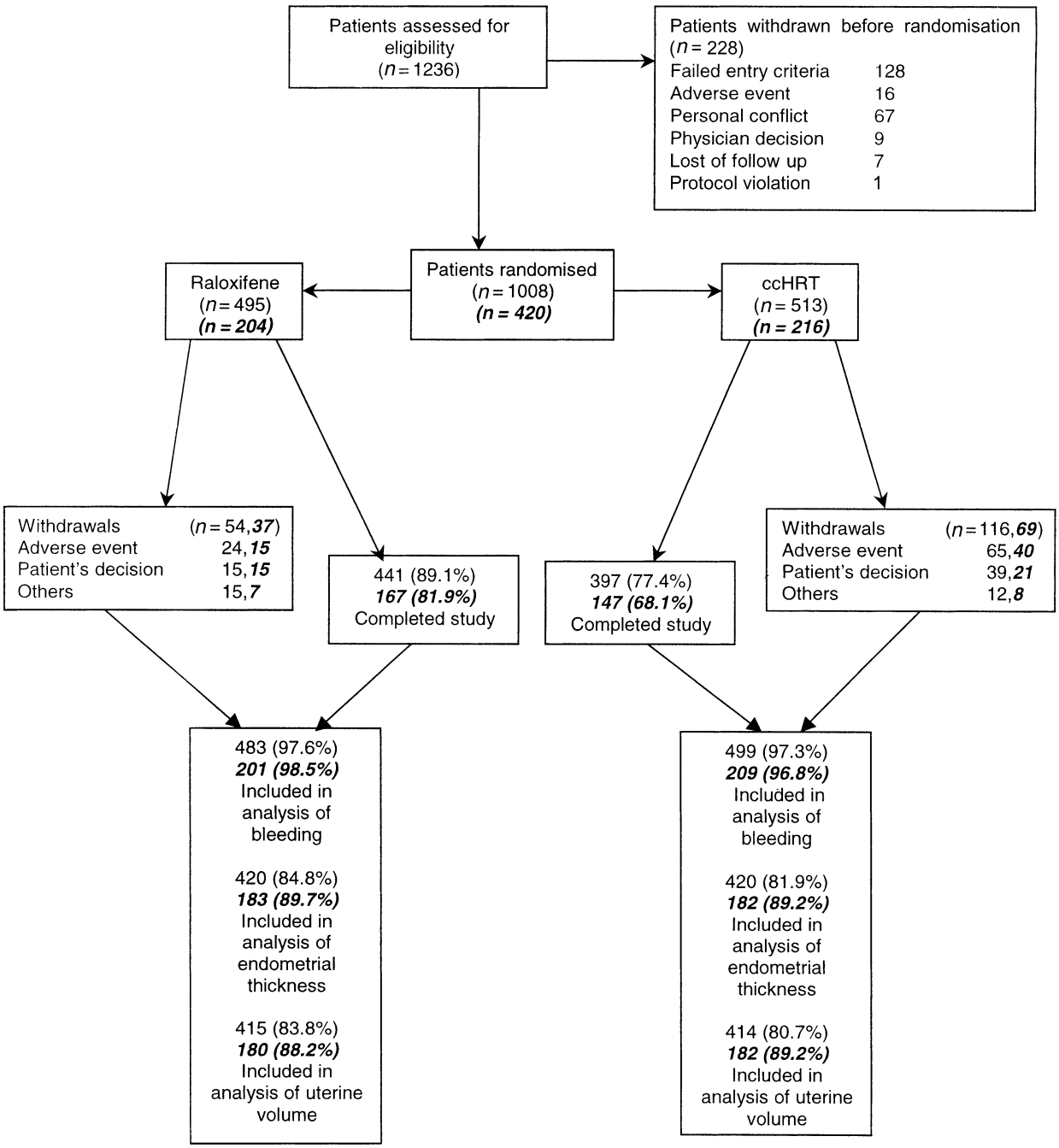

Fig. 1. Flow diagram of screened, randomised, withdrawn and analysed patients of the core phase (six months) and the ***extension phase (12 months)*** of the study.

Table 1. Baseline characteristics of Euralox 1 participants by treatment group ($n = 1008$). Values are expressed as n (%) or mean [SD].

Patient characteristics	Raloxifene	Continuous combined hormone replacement therapy	Total
n	495	513	1008
Caucasian	487 (98.4)	507 (98.8)	994 (98.6)
Age (years)	56.1 [4.8]	56.1 [4.9]	56.1 [4.9]
Years postmenopausal	7.1 [4.7]	7.2 [5.1]	7.1 [4.9]
Body mass index	25.7 [4.0]	26.1 [4.1]	25.9 [4.1]
Smokers	103 (20.8)	114 (22.2)	217 (21.5)

Four hundred and seventeen women (group A, 220 with raloxifene and 197 with continuous combined hormone replacement therapy) had an endometrial Pipelle biopsy at visit 1 and visit 4 and 38 women in group B (9 with raloxifene, 29 with continuous combined hormone replacement therapy) had an additional transvaginal ultrasonography/Pipelle biopsy performed at visit 3 and/or visit 4 as a result of repeated vaginal bleeding/spotting or an endometrial thickness >5 mm. Data on endometrial biopsies were not included in the primary efficacy analysis.

In both the core and extension phases, significantly more women on continuous combined hormone replacement therapy withdrew from the study ($P < 0.001$ and $P = 0.001$, respectively). Table 2 specifies the main reasons for discontinuation in the core phase of the study. The rate of early discontinuations as a result of adverse events or 'patient decision' differed significantly ($P < 0.001$ and $P = 0.001$, respectively) between groups, with higher rates in the continuous combined hormone replacement therapy group (12.7% and 4.8% for the continuous combined hormone replacement therapy and raloxifene groups for adverse events, respectively, and 7.6% and 3.0% for patient decision, respectively). Adverse events occurring in the core phase with an incidence of at least 2% for either drug or differing significantly ($P \leq 0.05$) between treatment groups are summarised in Table 3a. In the extension population, early discontinuation rates due to adverse events differed significantly (18.5% with continuous combined hormone replacement therapy and 7.4% with raloxifene, $P < 0.001$); the respective numbers for 'patient decision' were 9.7% and 7.4%; this difference was not significant ($P = 0.49$). Adverse events with observed statistically significant differences ($P \leq 0.05$) between treatment groups are summarised in Table 3b.

Table 4 gives the percentages of patients with bleeding in the single-blind placebo lead-in period and after randomisation. In the raloxifene group, bleeding was reported by 8.3% of patients in the lead-in period and 6.8% in the first six months after randomisation, while in the continuous combined hormone replacement therapy group, these figures were 7.0% and 55.1%, respectively. A total of 24.0% of all women in the continuous combined hormone replacement therapy group reported an average bleeding/spotting rate of more than 3 days/28 days, whereas only 0.2% of raloxifene users reported such vaginal bleeding pattern. Table 4 also shows the mean number of days of bleeding per 28 days in the first and second three month periods following randomisation. For continuous combined hormone replacement therapy, there is a statistically significant reduction ($P < 0.001$) over the course of the first six months and a significant increase over the baseline rate ($P < 0.001$ for each three month period compared with

Table 2. The main reasons leading to discontinuation during the core phase of the study (six months)*.

	Raloxifene	Continuous combined hormone replacement therapy	*P***
Adverse event	24 (4.8)	65 (12.7)	<0.001
Breast pain	0	19 (3.7)	<0.001
Vaginal haemorrhage	0	9 (1.8)	0.004
Thrombophlebitis	0	5 (1.0)	NS
Vasodilatation/menopause	6 (1.2)	2 (0.4)	NS
Weight gain	1 (0.2)	4 (0.8)	NS
Oedema	1 (0.2)	2 (0.4)	NS
Death	1 (0.2)	0	NS
Lost to follow up	7 (1.4)	5 (1.0)	NS
Personal conflict or patient decision	15 (3.0)	39 (7.6)	0.001
Physician's decision	2 (0.4)	2 (0.4)	NS
Protocol entry criteria not met	5 (1.0)	4 (0.8)	NS
Protocol violation	0	1 (0.2)	NS
Total	54 (10.9)	116 (22.6)	<0.001

NS = not significant.

* Adverse events and personal conflicts affecting three or more patients are listed.

** Fisher's exact test.

Table 3. Adverse events during study. Values are expressed as *n* (%).

	Raloxifene	Continuous combined hormone replacement therapy	*P**
(a) Adverse events with an incidence of at least 2% for either drug or differing significantly ($P \leq 0.05$) between treatment groups during the core phase of the study. Combining vasodilatation and menopause.			
Breast pain	9 (1.8)	136 (26.5)	<0.001
Flu syndrome	26 (5.3)	22 (4.3)	NS
Vasodilatation/menopause	33 (6.7)	7 (1.4)	<0.001
Headache	10 (2.0)	18 (3.5)	NS
Abdominal pain	10 (2.0)	15 (2.9)	NS
Vaginitis	14 (2.8)	11 (2.1)	NS
Cervix disorder	7 (1.4)	14 (2.7)	NS
Leg cramps	13 (2.6)	8 (1.6)	NS
Vaginal haemorrhage	0	19 (3.7)	<0.001
Weight gain	4 (0.8)	13 (2.5)	0.048
Emotional lability	0	7 (1.4)	0.015
(b) Adverse events with observed statistically significant differences between treatment groups ($P \leq 0.05$) for extension phase patients over the whole study.			
Breast pain	4 (2.0)	71 (32.9)	<0.001
Vasodilatation	13 (6.4)	3 (1.4)	0.009
Vaginal haemorrhage	0	7 (3.2)	0.015
Cervix neoplasm	0	7 (3.2)	0.015
Enlarged uterine fibroids	1 (0.5)	8 (3.7)	0.038

NS = not significant.
* Fisher's exact test.

baseline); there was no difference over the first six months for raloxifene users ($P = 0.58$). Table 5 shows predictors of bleeding/spotting within the continuous combined hormone replacement therapy and raloxifene groups. Younger age ($P = 0.008$), being a non-smoker ($P = 0.009$) and number of years into the menopause ($P = 0.062$) are predictive within the continuous combined hormone replacement therapy group. Within the raloxifene group, effects were significant for age ($P = 0.025$) and years postmenopausal ($P = 0.016$) but not for smoking ($P = 0.39$). Interactions between treatment and subgroup (Table 5) were statistically significant for age group and for years postmenopause and neared significance for smoking.

In the extension period, 26.1% of women on continuous combined hormone replacement therapy continued to experience bleeding, compared with 2.9% on raloxifene (Table 4). The proportion of women with an average bleeding/spotting rate of more than three days per month was 10.2% with continuous combined hormone replacement therapy and 0% with raloxifene. When comparing the

Table 4. Patients (%) with amenorrhoea and mean bleeding rate (days per 28 days) in Euralox 1 subjects by month. Months one to six: core phase; months seven to 12: extension phase (subset of study participants).

Month	Raloxifene			Kliogest		
	n	*n* (%) with no bleeding	Mean days bleeding per 28 days	*n*	*n* (%) with no bleeding	Mean days bleeding per 28 days
Baseline	**492**	**451 (91.7)**	**0.18**	**511**	**475 (93.0)**	**0.13**
1	480	468 (97.5)	0.07	494	354 (71.7)	1.79
2	477	471 (98.7)	0.03	479	317 (66.2)	2.99
3	474	464 (97.9)	0.04	457	306 (67.0)	2.72
1–3	**480**	**459 (95.6)**	**0.05**	**497**	**257 (51.7)**	**2.45**
4	454	464 (98.2)	0.05	420	334 (79.5)	1.74
5	449	442 (98.4)	0.07	416	329 (79.1)	2.01
6	447	435 (97.3)	0.09	408	311 (76.2)	1.77
4–6	**454**	**436 (96.0)**	**0.07**	**424**	**285 (67.2)**	**1.95**
1–6	**483**	**450 (93.2)**	**0.06**	**499**	**224 (44.9)**	**2.26**
7	175	172 (98.3)	0.03	157	133 (84.7)	1.56
8	175	173 (98.9)	0.06	155	135 (87.1)	1.10
9	171	170 (99.4)	0.01	153	134 (87.6)	1.03
10	171	171 (100)	0	149	136 (91.3)	0.81
11	171	171 (100)	0	147	135 (91.8)	0.63
12	167	167 (100)	0	147	133 (90.4)	0.56
7–12	**175**	**170 (97.1)**	**0.02**	**157**	**116 (73.9)**	**1.29**

Table 5. Comparison of proportions of patients with any bleeding or spotting during the treatment phase of the study by treatment group and by smoking status, age group and years postmenopause. Values are expressed as *n* (%) or *P*.

Subgroup	Treatment group	Raloxifene		Continuous combined hormone replacement therapy		Treatment × Subgroup interaction[†]
		Bleeding	No bleeding	Bleeding	No bleeding	
Smoking	Non-smokers	24 (6.3)	354 (93.7)	226 (58.2)	162 (41.8)	0.063
	Smokers	9 (8.6)	96 (91.4)	49 (44.1)	62 (55.9)	
		0.39[‡]		0.009[‡]		
Age group	<55 years	9 (4.6)	187 (95.4)	124 (60.2)	82 (39.8)	0.002
	55–60 years	13 (6.6)	183 (93.4)	112 (55.4)	90 (44.6)	
	≥61 years	11 (12.1)	80 (87.9)	39 (42.9)	52 (57.1)	
		0.025[‡]		0.008[‡]		
Years postmenopause	<6 years	11 (4.7)	224 (95.3)	144 (59.5)	98 (40.5)	0.003
	6–8 years	5 (5.2)	92 (94.8)	50 (52.1)	46 (47.9)	
	>8 years	17 (11.3)	134 (88.7)	81 (50.3)	80 (49.7)	
		0.016[‡]		0.062[‡]		

[†] From logistic regression model of log odds of bleeding with factors treatment group, subgroup and the interaction.
[‡] Fisher's exact tests for smoking; Mantel–Haenszel χ^2 tests within each treatment group for age group and years postmenopause group.

time course of bleeding in the extension subpopulation over the full study, continuous combined hormone replacement therapy users in this group bled on average for 1.93 days per month in months one to three, 1.92 days per month in months four to six and for 1.29 days per month in the second six months, a significantly lower rate in months seven to 12 compared with months four to six ($P = 0.022$). The respective rates for raloxifene users were 0.03, 0.02 and 0.02 days per month ($P = 0.81$ for the comparison of months four to six with months seven to 12). For the continuous combined hormone replacement therapy group, rates of bleeding were significantly greater in each of the three postbaseline periods compared with the baseline period ($P < 0.001$ in all cases) and compared with the respective rates seen with raloxifene ($P < 0.01$).

Following six months of raloxifene use, the mean endometrial thickness was not significantly changed from baseline [3.3 (1.3) mm *vs* 3.5 (1.7) mm] ($P = 0.11$), whereas continuous combined hormone replacement therapy [3.4 (1.4) mm *vs* 4.6 (2.1) mm] was associated with an increase in mean endometrial thickness of 1.2 (2.2) mm ($P < 0.001$). The difference between the treatment groups reached statistical significance ($P < 0.001$). Some 10.2% of raloxifene users had an increase of more than 2 mm in endometrial thickness, as compared with 27.6% of continuous combined hormone replacement therapy users. Smoking, age <55 years and <6 years postmenopausal were associated with changes in mean endometrial thickness in the continuous combined hormone replacement therapy group that were smaller than in non-smokers or older patients. In the continuous combined hormone replacement therapy group, similar increases in mean endometrial thickness were observed for patients with bleeding or spotting, as compared with those that had no bleeding or spotting. In the raloxifene group, those with bleeding or spotting had greater increases in mean endometrial thickness (mean increase of 1.1 mm) compared with those with no bleeding (mean increase of 0.1 mm). In the extension subgroup, the mean endometrial thickness in continuous combined hormone replacement therapy users was 4.4 (2.4) mm at the one year endpoint, which corresponded to a mean increase from baseline of 1.1 (2.4) mm ($P < 0.001$), whereas raloxifene users exhibited a non-significant decrease of 0.1 (1.4) mm, to 3.1 (1.3) at endpoint ($P = 0.98$). The difference between the groups in the change from baseline was significant ($P < 0.001$).

In the core study, mean uterine volume decreased from a mean of 31.4 (20.3) to 30.3 (16.2) mL ($P = 0.37$) in the raloxifene group; in the continuous combined hormone replacement therapy group, there was a significant increase ($P < 0.001$) from 31.3 (16.3) to 54.0 (36.1) mL and the difference between the compounds in the change in uterine volume reached significance ($P < 0.001$). In the extension subgroup, mean uterine volume at the one year endpoint was similar to those of the overall study population after six months [28.1 (16.2) mL for raloxifene and 56.2 (42.2) mL for continuous combined hormone replacement therapy; difference between the groups in change from baseline, $P < 0.001$].

DISCUSSION

The data of our large prospective and controlled study clearly show a distinct uterine safety and vaginal bleeding/spotting difference between two drugs currently in use for the treatment and prevention of postmenopausal osteoporosis. We directly compared the uterine and endometrial effects as well as the vaginal bleeding frequency of 6 and 12 months of continuous combined hormone replacement therapy with those of raloxifene. We found convincing evidence that, compared with a continuous combination of E_2 and norethisterone acetate (NETA), treatment with raloxifene does not lead to uterine bleeding, endometrial thickening and increase in uterine volume. All these parameters

remained essentially unchanged with raloxifene while increasing significantly with continuous combined hormone replacement therapy. In continuous combined hormone replacement therapy users, non-smoking and being in a younger age group were predictors of vaginal bleeding/spotting; mean changes in endometrial thickness were similar for those with and without vaginal bleeding/spotting. In the raloxifene group, however, greater age was associated with vaginal bleeding/spotting although the maximum frequency that appeared in the oldest age group was 12.1%. This age-related effect on bleeding frequency has never been reported in other raloxifene studies, but because of its low frequency, it is probably of little clinical significance.

The absence of endometrial proliferation, uterine growth and vaginal bleeding with long term raloxifene intake has previously been reported from several placebo-controlled clinical osteoporosis trials[6,8,11] of raloxifene. The placebo-controlled osteoporosis prevention trials with raloxifene[11] therapy for two years showed no endometrial or uterine stimulation. Likewise, the incidence of vaginal bleeding (3%) on raloxifene was the same as that for postmenopausal women receiving placebo. Similar findings have been reported from the Multiple Outcome Raloxifene Evaluation trial[8], a placebo-controlled osteoporosis treatment study including uterine safety data on 1936 postmenopausal women. Additionally, in this study, there was no evidence for an increased risk of endometrial hyperplasia among women who underwent regular endometrial biopsies.

Other studies with a shorter follow up period had uterine safety as their primary endpoint[12–17]; they compared raloxifene with placebo or hormonal replacement therapy regimen, commonly used in the US. One such study[17] compared the effects of 150 mg raloxifene and continuous conjugated equine oestrogens and medroxyprogesterone acetate on endometrial thickness, uterine volume, histologic characteristics of endometrial biopsies and bleeding in 139 postmenopausal women. After one year, both the mean endometrial thickness and uterine volume for the continuous combined hormone replacement therapy, but not for the raloxifene group, increased significantly over baseline. In contrast, the raloxifene group had a non-significant decrease in mean uterine volume. In 9% of the women on continuous combined hormone replacement therapy, vaginal bleeding led to discontinuation, while in the raloxifene group, there was no discontinuation as a result of vaginal bleeding. The study also demonstrated that after one year of therapy, raloxifene did not have tamoxifen-like uterine effects, and no endometrial hyperplasia or polyp formation was observed in this study. In contrast, tamoxifen was associated with an 18% incidence of endometrial hyperplasia and 25–30% endometrial polyp formation[10]. The two year results of this trial[16] showed an endometrial stimulation of 5.6% with 150 mg raloxifene, whereas this was in 21.3% with continuous combined hormone replacement therapy. In a meta-analysis combining results from separate randomised trials of 722 women receiving various doses of raloxifene, Cohen *et al.*[13] compared endometrial safety and uterine bleeding data. The incidence of vaginal bleeding and increased endometrial thickness was not significantly different for all doses of raloxifene and for the placebo groups.

Although continuously added progestins are needed to minimise the endometrial cancer risk[18] associated with oestrogen replacement therapy, it is well known that continuous combined hormone replacement therapy is associated with unpredictable slight vaginal spotting or bleeding (varying from 50% to 80%), especially in the first 12 months. Dropout rates of up to 65% have been reported. Fewer women experience bleeding after 12 months of treatment but this low rate of vaginal spotting may be due to self-selection bias by dropouts. In the placebo-controlled Postmenopausal Oestrogen/Progesterone Intervention trial, continuous combined regimen given for three years, using conjugated equine oestrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) daily, led to bleeding/spotting in 63% in the first six-cycle interval; 45%, 57%, 44%, 57% and 37% bled/spotted in the subsequent six-cycle intervals[3].

Testosterone-derived progestins have been suggested to have more potent progesterone-like effects on the endometrium than progesterone-derived progestins[19]. In our study, women treated with E_2 + NETA bled in 55.1% of cases. Although the percentage of patients with bleeding declined during the course of the study, the bleeding rate per month remained significantly elevated when compared with the baseline values obtained during the placebo lead-in period. These findings are in good agreement with those of the only published data on continuous combined hormone replacement therapy and incidence of vaginal bleeding. In a prospective, randomised, double-blind clinical trial of 100 postmenopausal women, Dören *et al.*[20] compared tibolone with a combination of 2 mg E_2 + 1 mg NETA with respect to the incidence of uterine bleeding; they demonstrated that 59.2% in the E_2 + NETA group reported vaginal bleeding episodes. The same authors also published on changes in endometrial thickness and uterine volume on continuous combined hormone replacement therapy. After one year of follow up, there was a significant increase in mean endometrial thickness from 2.58 (1.04) to 3.07 (1.68) mm. These authors also noted an increase in uterine volume on continuous combined hormone replacement therapy.

An increase in endometrial thickness and uterine volume reflects an increase in oestrogenicity with continuous combined hormone replacement therapy which in the long term can cause endometrial and myometrial growth leading to abnormal vaginal bleeding (low compliance to treatment), endometrial polyp and myometrial fibroid formation. The combination of abnormal vaginal bleeding with endometrial thickening will also increase intrauterine diagnostic testing using saline infusion sonography, hysteroscopy or dilation and curettage, and weaken the cost–benefit effect of continuous combined hormone replacement therapy for the prevention and treatment of osteoporosis.

The strengths of our study are its prospective design starting with a normal baseline endometrium, the central reading of all transvaginal ultrasonography images by one person in a blinded fashion and the recording of vaginal bleeding/spotting in a carefully kept diary. However, the study also has two limitations. Firstly, continuous combined hormone replacement therapy formulations containing lower doses of oestrogen than the dose tested in this study have become available in the meantime. While the bleeding rates of such formulations are well below the ones reported here, bleeding is still a common event, and it is unlikely that the treatment-specific differences *vs* raloxifene observed here would have disappeared in a study using a lower oestrogen dose as comparison. Besides, in 1997 when this trial was initiated, these formulations were not yet widely available, and the continuous combined hormone replacement therapy formulation used here was one of the gold standards in Europe, and is still widely prescribed today. The second limitation involves the selection of the patient population for this study. For ethical reasons, only women with an expected benefit from either study drug were eligible. This provision required the absence of a history of breast cancer (because of the continuous combined hormone replacement therapy arm), severe vasomotor symptoms (because of the raloxifene arm) and thromboembolic events (because of both treatments), as well as the presence of risk factors for osteoporosis and/or cardiovascular disease. In light of the recently published data from large prospective studies which no longer support the use of hormonal replacement therapy to prevent cardiovascular disease (HERS, ERA, WHI[18,21,22]), the rationale of including women at increased cardiovascular risk seems questionable in retrospect; however, it should be remembered that in 1997 none of these data were available.

From the results of the current study, it must be concluded that the effects of raloxifene on endometrial thickness, uterine volume and incidence of vaginal bleeding are clearly more favourable than those of E_2 + NETA.

Acknowledgements

Patrick Neven and Thomas Nickelsen initiated the project and contacted the investigators for participation. All authors participated in the writing committee. Deborah Quail did all statistical analyses.

The authors would like to thank Mr Tero Laulajainen and Mrs Antje Hottgenroth for their invaluable help in central study co-ordination and Mrs Greet Van Brabant for data management. The study described in this report was sponsored by Eli Lilly.

Investigators for the Euralox 1 trial:

Belgium: Dr Patrick Neven, Algemene Kliniek St Jan, Brussels (Principal Investigator); Dr Mireille Smets, Cliniques Universitaires Saint-Luc, Brussels; Dr Rudy Gevers, Akademisch Ziekenhuis VUB-Jette, Brussels; Dr Guido Vanderick, Algemene Kliniek St Jan, Brussels; Dr Frederic van den Brul, CHU Sart Tilman, Liège; Professor Herman Depypere, UZ-Gent; **Denmark:** Dr Sven Skouby, Frederiksberg Hospital, Frederiksberg; Dr Anette Peen, Speciallaegernes Hus, Aarhus; Dr Lars Andersen, Sygehus Hillerod; Dr Torben Philipsen, Centralsygehus Holbaek; Dr Birger Moller, Universitetshospital Odense; Dr Erik Poulsen, Odense; Dr Lars-Olof Abrahamsson, Hvidovre; Dr Anne Jessen, Sonderborg; Professor Bent Ottesen, Hvidovre Hospital, Hvidovre; Dr Jens Lyndrup, Amtssygenhus, Roskilde; **Finland:** Professor Aila Tiitinen, Helsingin Yliopistollinen Keskussairaala, Helsinki; Professor Tuula Salmi, Turun Yliopistollinen Keskussairaala, Turku; Professor Risto Tuimala, Tampereen Yliopistollinen Keskussairaala, Tampere; Professor Ulla Puistola, Oulun Yliopistollinen Keskussairaala, Oulu; Dr Jukka Puolakka, Keski-suomen Keskussairaala, Jyväskylä; Dr Tarja Jarvi, Hemo Ov, Laakariasema, Lahti; Dr Pentti Kilkku, Torilinnan Laakariasema, Pori; Dr Marjo Tuppurainen, Kuopion Yliopistollinen Keskussairaala, Kuopio; **France:** Dr Marc Levrier, Talence; Dr Monique Commenges, Centre Hospitalier Pellegrin Tripode, Bordeaux; Dr Veronique Kerlo, Nantes; Dr Lucien Chaby, Centre de Santé Jack Senet, Paris; Dr Michèle Scheffler; Nancy; Dr Veronique Pascal, Hôpital Brabois, Vandoeuvre Nancy; Prof. Patrick Madelenat, Hôpital Bichat, Paris; Dr Charles Nahmanovici, Nice; Dr Francoise Mousteou, Cagnes-sur-Mer; Dr Dominique Crestinu, Paris; Dr Dominique Wiel-Masson, Chartres; Dr Alain Audebert, Bordeaux; Professor Gerard Mage, Hôtel Dieu, Clermont-Ferrand; Dr Aliette Siboni-Frisch, Toulouse; Dr Marie-Hélène Cayrol, Clinique St Jean de Languedoc, Toulouse; Dr Isabelle Zordan-Ducasse, Toulouse; Dr Martine Gelas, Lyon; Dr Pascale Mirakian, Clinique Montplaisir, Lyon; Dr Bruno Mazenod, Hôpital de l'Antiquaille, Lyon; Dr Colette Ferrand-Desneiges, Rouen; Dr Martine Pollack, Grenoble; Dr Nicole Douay, Villeneuve d'Ascq; Dr Katty Ardaens, Seclin; Dr Francis Sailly, Tourcoing; Dr Martine Perdrix, Clinique Médical Mgen, Lyon; **Greece:** Professor George Creatsas, Aretaieio Hospital, Athens; **Ireland:** Dr Maire Milner, Rotunda Hospital, Dublin; Professor John Bonnar, St James's Hospital, Dublin; **Israel:** Professor Zion Ben-Rafael, Rabin Medical Center, Petah Tiqva; Dr Yair Frenkel, Chaim Sheba Medical Center, Tel-Hashomer; Dr Nahman Eckstein, Ichilov Hospital, Tel-Aviv; Dr Eitan Pe'er, Rambam Medical Center, Haifa; **Italy:** Professor Carlo Campagnoli, Ospedale Ginecologico S. Anna, Torino; Professor Pierluigi Benedetti-Panici, Libero Istituto Universitario, Roma; Professor Carmine Nappi, Universitá Federico II, Napoli; Professor Annibale Volpe, Policlinico Universitario, Modena; Professor Alberto Bacchi, Clinica Ostetrica e Ginecologica dell'Universitá, Parma; Professor Domenico de Aloysio, Clinica Ginecologica ed Ostetrica dell'Universitá, Bologna; Professor Vincenzo Giambanco, Ospedale Civico E. Benfratelli, Palermo; Professor Costante Donati Sarti, Policlinico

Monteluce, Perugia; Professor Sergio Schonauer, Policlinico Universitario, Bari; Professor Secondo Guaschino, Istituto Burlo Garofolo, Trieste; **Netherlands:** Dr J. Schram, Drechtsteden Ziekenhuis, Zwijndrecht; Dr W. Stroobants, St Jozef Ziekenhuis, Kerkrade; Dr H. The, St Gemini Ziekenhuis, Den Helder; Dr A. Broekman, Twesteeden Ziekenhuis, Waalwijk; Dr T. M. Hameeteman; St Antonius Ziekenhuis, Nieuwegein; Dr Beth Morrel, Ikazia Ziekenhuis, Rotterdam; Dr Tjeerd D Ypma, Scheper Ziekenhuis, Emmen; Dr Leen Pijpers, Albert Schweitzer Ziekenhuis, Dordrecht; Dr Lodewijk J Bosch van Drakenstein, Flevoziekenhuis, Almere; **Norway:** Dr B. Eriksen, Haugesund Gyn Klinikk, Haugesund; Dr Hans Ejner Ipsen, Volvat Legesenter, Alesund; Dr Terje Soerdal, Spesialistlegesenteret, Trondheim; Dr Gunnar Nordland, Faber Swensson & Nordland, Kristiansund; Dr Tore Lunde, Larvik; Dr Randi Simes Dugal, Sandefjord; Dr Oeyvin Skarra, Osteoporoselaboratoriet, Oslo; Dr Tor Loevset, Bergen; Dr Unn Baerug, Halden; **Poland:** Dr Romuald Debski, Klinika Ginekologii Poloznictwa Cmkp, Warszawa; Professor Alina Warenik-Szymankiewicz, Katedra Endokrinologii Ginekologicznej, Poznan; Dr Violetta Skrzypulec-Ciszek, IV Katedra i Klinika Poloznictwa i Ginekologii, Tychy; Dr Tomasz Rechberger, II Katedra Poloznictwa i Chorób Kobiecych, Lublin; Professor Tomasz Pertynski, Oddzial Kliniczny Chorób Menopausy; Lódz; Professor Jerzy Mielnik, I Klinika Poloznictwa i Ginekologii A.M., Gdansk; Professor Stanislaw Rozewicki, Klinika Ginekologii, Szczecin; **Portugal:** Dr Fernanda Aguas, Maternidade Bissaya Barreto, Coimbra; Dr Ana Fatela, Maternidade Dr Alfredo da Costa, Lisboa; Professor Madalena Botelho, Hospital de Santa Maria, Lisboa; Dr Isabel Amaral, Hospital Nossa Senhora do Rosário, Barriero; Dr Olga Viseu, Hospital Distrital, Faro; Professor Martinez Oliveira, Hospital de Sao Joao, Porto; Dr Ana Pinho, Garcia da Orta, Almada; Professor Henrique Oliveira, Hospitais da Universidade, Coimbra; **Romania:** Professor Bogdan Marinescu, Clinical Hospital of Obstetrics and Gynecology, Bucuresti; Professor Decebal Hudita, Spitalul Clinic Cantacuzino, Bucuresti; Professor Florin Stamatian, Clinic of Gynecology Dr Stanca, Cluj; **South Africa:** Dr F. Grobler, Medfem Clinic, Sandton; Dr Pierre Davis, Little Company of Mary Medical Centre, Pretoria; Dr Tobie Devilliers, Panorama Medical Clinic, Cape Town; **Spain:** Dr Camil Castelo-Branco, Hospital Clinic I Provincial, Barcelona; Dr Montserrat Manubens, Institut Dexeus, Barcelona; Dr Joaquin Calaf, Hospital Santa Creu i Sant Pau, Barcelona; Dr Albert Cabero, Ciutat Sanitaria de la Vall D'Hebron, Barcelona; Dr José L. Duenas-Diez, Hospital Universitario Virgen Macarena, Sevilla; Dr Antonio Cano, Hospital Clínico Universitario, Valencia; **Sweden:** Professor Torbjörn Bäckström, Norrlands Universitetssjukhus, Umea; Dr Staffan Nilsson, Falu Lasarett, Falun; Dr Lars-Ake Mattsson, Sahlgrenska Univ/Östra, Göteborg; Dr Göran Berg, Universitetssjukhuset, Linköping; Professor Britt Marie Landgren, Karolinska Sjukhuset, Stockholm; Professor Göran Samsioe, Universitetssjukhuset, Lund; **Switzerland:** Professor Paul J. Keller, Universitätsspital, Zürich; Dr Christian de Geyter, Kantonsspital, Basel; Professor Martin Birkhauser, Inselspital, Bern; **Turkey:** Professor Cihat Unlu, University Department of Gynecology and Obstetrics, Ankara; Professor Erdogan Ertungealp, I.U. Cerrahpasa Medical Faculty, Istanbul; Professor Mithat Erenus, Marmara University, Istanbul; Professor Abdullah Turfanda, I.U. Istanbul Medical Faculty, Istanbul; **United Kingdom:** Dr M. Stone, Llandough Hospital, South Glamorgan; Dr Timothy Hillard, Poole Hospital NHS Trust, Poole; Dr Michael Cust, City General Hospital, Derby; Dr John B. Paling, Nuffield Hospital, Birmingham; Dr S. H. Taylor, Synexus Clinical Research Unit, Chorley.

References

1. Barrett-Connor E. Hormone replacement therapy. *BMJ* 1998;**317**: 457–461.
2. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;**288**:321–333.
3. Legault C, Slone S, Judd H. Bleeding patterns over 3 years in postmenopausal women taking placebo or four different combinations of oestrogens and progestins. The PEPI trial. *Menopause* 1999;**6**: 325–326.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108411 women without breast cancer. *Lancet* 1997;**350**: 1047–1059.
5. Love R, Barden H, Mazess R, et al. Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Arch Intern Med* 1994;**154**:2585–2588.
6. Ettinger B, Black D, Mitlak B, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999; **282**:637–644.
7. Fisher B, Costantino J, Wickerham D, et al. Tamoxifen for the prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998;**90**: 1371–1388.
8. Cummings S, Eckert S, Krueger K, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women. *JAMA* 1999;**281**: 2189–2197.
9. IBIS investigators. First results from the International Breast Cancer Intervention Study (IBIS-I). *Lancet* 2002;**360**:817–824.
10. Neven P, Vernaeve H. Guidelines for monitoring patients taking tamoxifen treatment. *Drug Saf* 2000;**22**:1–11.
11. Delmas P, Bjarnason N, Mitlak B, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;**337**:1641–1647.
12. Davies GC, Huster WJ, Shen W, et al. Endometrial response to raloxifene compared with placebo, cyclical hormone replacement therapy, and unopposed estrogen in postmenopausal women. *Menopause* 1999; **6**:188–195.
13. Cohen F, Watts S, Shah A, et al. Uterine effects of 3-year raloxifene therapy in postmenopausal women younger than age 60. *Obstet Gynecol* 2000;**95**:104–110.
14. Goldstein S, Scheele W, Rajagopalan S. A 12-month comparative study of raloxifene, estrogen, and placebo on the postmenopausal endometrium. *Obstet Gynecol* 2000;**95**:95–103.

15. Boss S, Huster W, Neild J, et al. Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. *Am J Obstet Gynecol* 1997;**177**:1458–1464.
16. Fugere P, Scheele W, Shah A, et al. Uterine effects of raloxifene in comparison with continuous-combined hormone replacement therapy in postmenopausal women. *Am J Obstet Gynecol* 2000;**182**:568–574.
17. Jolly EE, Scheele WH, et al. A high dose of raloxifeneHCl is not stimulatory in the uterus of healthy postmenopausal women [abstract]. IV European Congress on Menopause Abstract Book, 1997 October 8–12, Vienna, Austria. Paris, FR: Editions ESKA, 1997:68 (Abstract no. FC5-8).
18. Larkin M. Ups and downs for HRT and heart disease. *Lancet* 2000;**355**:1338.
19. Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999;**13**:1131–1137.
20. Dören M, Rübig A, Coelingh Bennink HJT, et al. Impact on uterine bleeding and endometrial thickness: tibolone compared with continuous combined estradiol and norethisterone acetate replacement therapy. *Menopause* 1999;**6**:299–306.
21. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–613.
22. Herrington DM, Reboussin DM, Brosnihan B, et al. Effects of estrogen replacement on the progression of coronary artery atherosclerosis. *N Engl J Med* 2000;**343**:522–529.

Accepted 12 November 2002