Reduced vaginal bleeding in postmenopausal women who receive combined norethindrone acetate and low-dose ethinyl estradiol therapy versus combined conjugated equine estrogens and medroxyprogesterone acetate therapy

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OBJECTIVE: The purpose of this study was to compare the effects on vaginal bleeding patterns of continuous combined hormone replacement therapy with norethindrone acetate and ethinyl estradiol versus conjugated equine estrogens and medroxyprogesterone acetate.

STUDY DESIGN: Three hundred fifty-seven postmenopausal women were selected randomly (in a blinded manner) to 12 months of treatment with 1 mg norethindrone acetate/5 μg ethinyl estradiol, placebo, or open-label 0.625 mg conjugated equine estrogens/2.5 mg medroxyprogesterone acetate (conjugated equine estrogens/medroxyprogesterone acetate [CEE/MPA]; Prempro). The incidence and duration of vaginal bleeding were assessed throughout the study. Statistical analyses used Cochran-Mantel-Haenszel methodology and analysis of variance.

RESULTS: At 3 months, 1 mg norethindrone acetate/5 μg ethinyl estradiol therapy reduced the incidence of bleeding (12% vs 23%; $P < .029$) and bleeding and/or spotting (22% vs 44%; $P < .001$), compared with conjugated equine estrogens/medroxyprogesterone acetate therapy. The mean duration of bleeding and bleeding and/or spotting were also reduced with 1 mg norethindrone acetate/5 μg ethinyl estradiol therapy versus conjugated equine estrogens/medroxyprogesterone acetate ($P = .004$ and $P < .001$, respectively). The incidence of cumulative amenorrhea at every monthly interval was significantly better with 1 mg norethindrone acetate/5 μg ethinyl estradiol therapy versus conjugated equine estrogens/medroxyprogesterone acetate therapy ($P < .05$). Associated adverse event (ie, headache, breast pain) incidence rates were similar in the 2 active treatment groups.

CONCLUSION: The 1 mg norethindrone acetate/5 μg ethinyl estradiol therapy provides significantly better control of vaginal bleeding than conjugated equine estrogens/medroxyprogesterone acetate therapy at all time points investigated in this 12-month study. (Am J Obstet Gynecol 2003;188:92-9.)

Key words: Hormone replacement therapy, vaginal bleeding, norethindrone acetate, ethinyl estradiol, cumulative amenorrhea

The efficacy of hormone replacement therapy (HRT) in the relief of acute menopause-related symptoms[1,2] and the prevention of osteoporosis is well established.[3] Evidence also suggests that HRT has potential cardiovascular[3,4] and cognitive function benefits,[5,6] although these claims remain controversial.[7,8] Because the benefits of HRT are rapidly lost after discontinuation of therapy, long-term treatment is recommended.

Women who receive HRT often discontinue therapy in the first year,[9-11] which indicates a need for improvements in the tolerability profiles of existing products. Rates of discontinuation can be as high as 68% within the first year of treatment[12]; in many cases, discontinuation occurs within the first 3 to 6 months of therapy.[10,11] Many factors influence adherence to HRT regimens.[9] However, most patients who discontinue therapy do so because of undesired vaginal bleeding.[13,14] The menses-like withdrawal bleeding that is experienced by women tho take cyclic regimens is a major barrier to continued use.[15,16] Continuous combined HRT (CCHRT), which consists of daily estrogen and progestin, was developed to improve patient adherence by reducing bleeding episodes. Al-

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Supported by Pfizer Global Research & Development.

Received for publication February 14, 2002; revised May 9, 2002; accepted August 4, 2002.

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0002-9378/2003 $30.00 + 0

doi:10.1067/mob.2003.104

though regular withdrawal bleeding does not occur, these products can be associated with unpredictable vaginal bleeding and spotting, particularly during the early months of treatment.[15] Nevertheless, there is evidence to suggest that patient adherence to CCHRT is improved in comparison with cyclic regimens.[14] In a population-based study, adherence during the first year after the initial prescription was 54.4% among users of cyclic regimens and 68.9% among CCHRT users.[13] Controlled comparative analyses of the bleeding profiles of different CCHRTs have been reported rarely, which makes it difficult for the physician to compare agents and to tailor treatment to individual patients.[15-20] Differences between CCHRTs have been observed with respect to a variety of amenorrhea parameters over relatively short-term exposure,[20] but longer-term effects have not been reported. Furthermore, many published studies do not report the incidence of cumulative amenorrhea, although this parameter provides an estimate of when a woman will become and remain amenorrheic, and is therefore of the greatest value to both physicians and patients. The sooner a woman becomes permanently amenorrheic, the greater the likelihood that she will continue to undergo therapy.

The combination of 1 mg norethindrone acetate and 5 μg ethinyl estradiol (1/5 NA/EE) is a recently introduced CCHRT. The present placebo-controlled study was designed to measure bleeding patterns that are associated with 1/5 NA/EE treatment versus conjugated equine estrogens and medroxyprogesterone acetate (CEE/MPA) over 12 months. Results at 6 months have been previously reported.[20]

Material and methods

Study design. This was a placebo-controlled, parallel-group, multicenter (57 sites) study of 12-month duration. After a 4-week screening period, women who were eligible entered a 12-month treatment period and were randomly assigned to 1 of 8 parallel treatment groups (Fig 1). All NA/EE groups and placebo treatment were double-blinded; the CEE/MPA control arm was open-label. A detailed description of this study design has been previously published.[20] Although 4 NA/EE dosage combinations were assessed, the present report focuses solely on 1/5 NA/EE and CEE/MPA versus placebo arms. Of the 357 subjects who were assigned randomly to a treatment group in this study, 354 subjects received at least 1 dose of study medication and were therefore eligible for inclusion in the efficacy analysis.

During treatment, women were instructed to take 1 study medication tablet per day in the evening and 1000 mg of calcium daily. Subjects kept daily diaries of menopausal symptoms and vaginal bleeding or spotting. Vaginal bleeding was defined as bleeding that required sanitary protection (ie, the use of a tampon or sanitary pad) to prevent saturation of underwear; spotting was defined as vaginal bleeding that did not require the use of sanitary protection.

All sites obtained Institutional Review Board approval of the protocol and its amendments, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each subject before enrollment.

Inclusion and exclusion criteria. Women of any race, who were at least 40 years of age, had an intact uterus, had undergone either spontaneous or surgical menopause within 5 years before the start of the study, and had been amenorrheic for at least 6 months, were eligible to enroll. Serum follicle-stimulating hormone and estradiol concentrations of ≥50 mIU/mL and ≤20 pg/mL, respectively, were a prerequisite to study inclusion for all women who had previously been amenorrheic for 6 to 12 months. In addition, all subjects were required to have a body mass index ≤31 kg/m^2.

Study exclusion criteria included the use of orally administered sex hormones (estrogens, progestins, androgens) within 8 weeks before entering the study, or the use of transdermal hormone therapy within 4 weeks before enrollment. Additionally, the use of the following drugs was prohibited: chronic use of systemic corticosteroids, anticonvulsants, calcium in excess of the provided daily supplement, fluoride in excess of 1 mg per day, supplemental vitamin A or D, or any other medication that may have affected bone calcium metabolism; lipid-lowering drugs; antiresorptive medications; hepatic enzyme inducers; herbal teas; and phytoestrogens. Further exclusion criteria included a history of significant intercurrent or concurrent disease; mammogram results that are suggestive of malignant disease; vasomotor symptoms that required medical treatment; a history or evidence of any previous fracture of the hip or spine; current vaginal bleeding, regardless of suspected cause; diseases that affect bone metabolism; bisphosphonate use within the previous 10 years or calcitonin use within the previous 6 months; and HRT contraindication.

Efficacy assessments. The primary outcome measure of the study was incidence of endometrial hyperplasia (data on file, Pfizer Global Research and Development, 2002). Secondary outcome measures that are discussed in this report include the incidence of amenorrhea, cumulative amenorrhea, bleeding and/or spotting, and duration of bleeding and/or spotting. Duration of bleeding was defined as the number of days of bleeding in a 30-day time period (month).

Amenorrhea and bleeding/spotting were assessed from subject diaries that were collected at the end of months 3, 6, and 12. Incidence of bleeding and/or spotting was based on entries in subjects' daily diaries. Any incidence of bleeding or spotting in each 30-day period

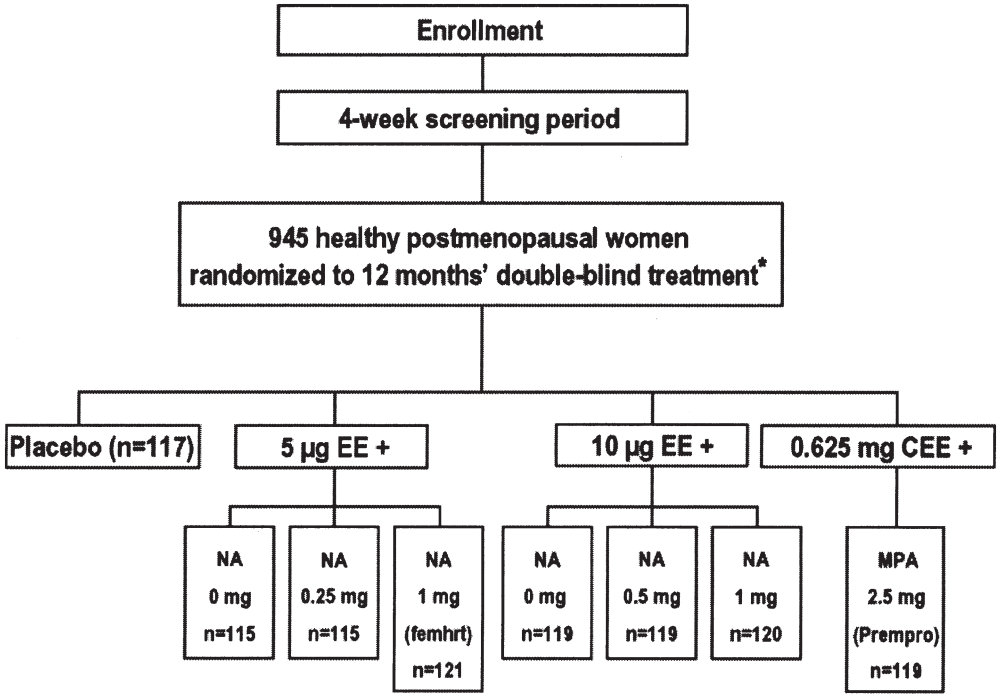

Fig 1. Study overview. The *asterisk* denotes that all treatment arms were blinded, with the exception of the CEE/MPA arm, which was open-label.

resulted in the inclusion of an individual subject in the assessment. Amenorrhea was defined as the absence of bleeding and/or spotting for the duration of a 30-day period, with incidence of amenorrhea measured as the percentage of subjects who remained amenorrheic throughout that period. Cumulative amenorrhea was defined as the monthly cumulative percentage of subjects achieving amenorrhea in that month and who remained amenorrheic for the remainder of the 12-month study.

Safety assessments. Safety assessments were based on clinical laboratory changes at the beginning and end of the study, a physical and pelvic examination before and after the study, and adverse events both during the screening and the treatment phases.

Statistical analyses. The primary efficacy analyses used data from the intent-to-treat population, which was defined as all subjects who were randomly assigned and who received at least 1 dose of study medication, with the last observation carried forward. All testing was performed at $\alpha = .05$. The primary time point for the assessment of the incidence of amenorrhea, bleeding, and bleeding and/or spotting was month 3. Analyses were obtained with Cochran-Mantel-Haenszel analysis and were stratified by center. The duration of bleeding and bleeding and/or spotting were assessed at month 3 with analysis of variance with terms for treatment and center. Secondary analyses, which were performed at months 1, 2, and 4 through 12, were the same as the analyses that were carried out at month 3.

The sample size calculation was based on the expected difference in the occurrence of the primary outcome parameter, endometrial hyperplasia. It was assumed to be 8% in the unopposed 5 µg EE group and 0% in the 1/5 NA/EE group. At $\alpha = .05$ and a power of 0.90, a sample size of 124 subjects per group was required.

Results

Baseline characteristics. In total, 357 healthy postmenopausal women were randomly assigned to treatment with placebo (n = 117), 1/5 NA/EE (n = 121), or CEE/MPA (n = 119). There were no observed differences overall among the treatment groups at baseline (Table I).

Bleeding incidence. The 1/5 NA/EE group had a significantly lower incidence of bleeding than the CEE/MPA group at months 1, 2, 3, 6, and 7. At the primary time point of month 3, the incidence of bleeding in the 1/5 NA/EE group versus the CEE/MPA group was 12% versus 23% ($P = .029$; Table II). Additionally, the incidence of bleeding in the 1/5 NA/EE group was statistically indistinguishable from the incidence in the placebo group at months 4, 5, and 7 through 12 (Fig 2).

Incidence of bleeding and/or spotting. The 1/5 NA/EE group had a significantly lower incidence of bleeding and/or spotting than the CEE/MPA group for all 12 months of the study, except for month 5. At month 3, the incidence of bleeding and/or spotting in the 1/5 NA/EE group versus the CEE/MPA group was 22% versus 44% ($P < .001$; Table II). Incidence rates for bleeding and

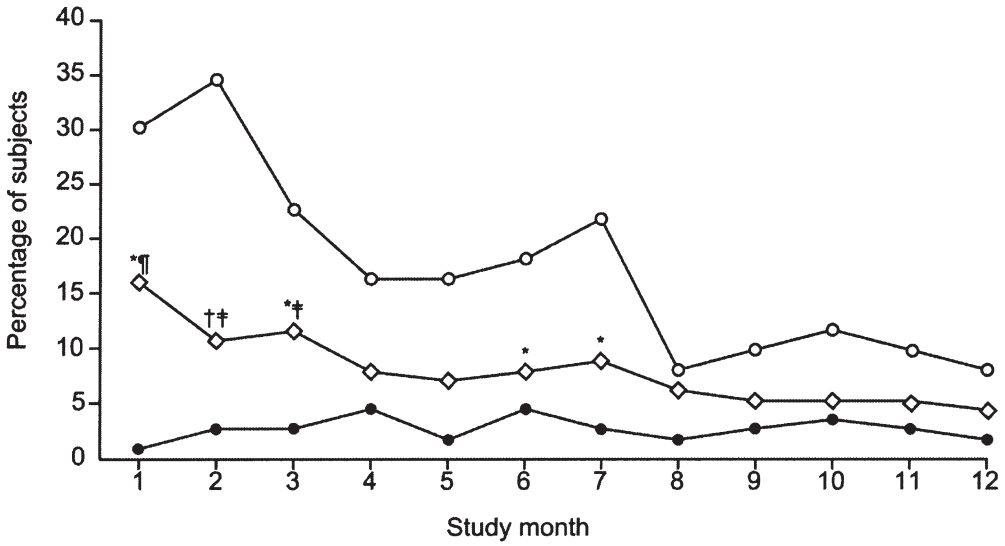

Fig 2. Percentage of subjects with bleeding, intent-to-threat/last observation carried forward population. The *asterisk* denotes $P < .05$; the *dagger* denotes $P < .001$, compared with CEE/MPA; the *double dagger* denotes $P < .05$; the *paragraph symbol* denotes $P < .001$, compared with placebo. Significance was not calculated at month 6. The data are based on Cochran-Mantel-Haenszel (general association) test stratified by center. The *closed circles* represent placebo; the *open diamonds* represent 1/5 NA/EE; and the *open circles* represent CEE/MPA.

Table I. Subject baseline characteristics

Characteristic	*Placebo*	*1/5 NA/EE*	*CEE/MPA*
Randomized to treatment (No.)	117	121	119
Age (y)*	51.3 (3.9)	51.6 (4.2)	51.4 (3.8)
Months since last menstrual period*	31.9 (17.6)	32.6 (19.6)	32.1 (16.1)
Race (No.)			
White	98 (84%)	111 (92%)	99 (83%)
Black	11 (9%)	4 (3%)	8 (7%)
Hispanic	2 (2%)	2 (2%)	8 (7%)
Other	6 (5%)	4 (3%)	4 (3%)
Physical activity (No.)			
Sedentary	33 (28%)	23 (19%)	24 (20%)
Moderately active	64 (55%)	78 (64%)	75 (63%)
Highly active	19 (16%)	20 (17%)	20 (17%)
Smoking status (No.)			
Never smoked	56 (48%)	53 (44%)	60 (50%)
Past smoker	30 (26%)	36 (30%)	31 (26%)
Current smoker†	31 (26%)	32 (26%)	28 (24%)
Light	12 (39%)	13 (41%)	5 (18%)
Moderate	12 (39%)	15 (47%)	16 (57%)
Heavy	7 (23%)	4 (13%)	7 (25%)
Blood pressure (mm Hg)*			
Systolic	116.8 (14.3)	118.4 (15.8)	119.5 (15.8)
Diastolic	74.1 (8.8)	73.5 (9.3)	74.7 (8.7)
Body mass index (kg/m^2)*	26.0 (3.5)	25.5 (3.4)	25.6 (3.7)

*Data are given as mean.
†*Light*, 1-10 cigarettes/day; *moderate*, 11-20 cigarettes/day; *heavy*, > 21 cigarettes/day.

bleeding and/or spotting among the 1/5 NA/EE group were statistically indistinguishable from those in the placebo group in the last 5 months of the study (Fig 3).

Duration of bleeding and/or spotting. The 1/5 NA/EE group experienced significantly fewer days per month of bleeding and/or spotting for all 12 months of the study than did the CEE/MPA group. At month 3, the mean duration of bleeding and/or spotting was significantly shorter in the 1/5 NA/EE group than in the CEE/MPA group (1.7 days per month vs 4.1 days per month; $P < .001$). The duration of bleeding and/or spotting in 1/5 NA/EE group at months 3 through 6 and 8 through

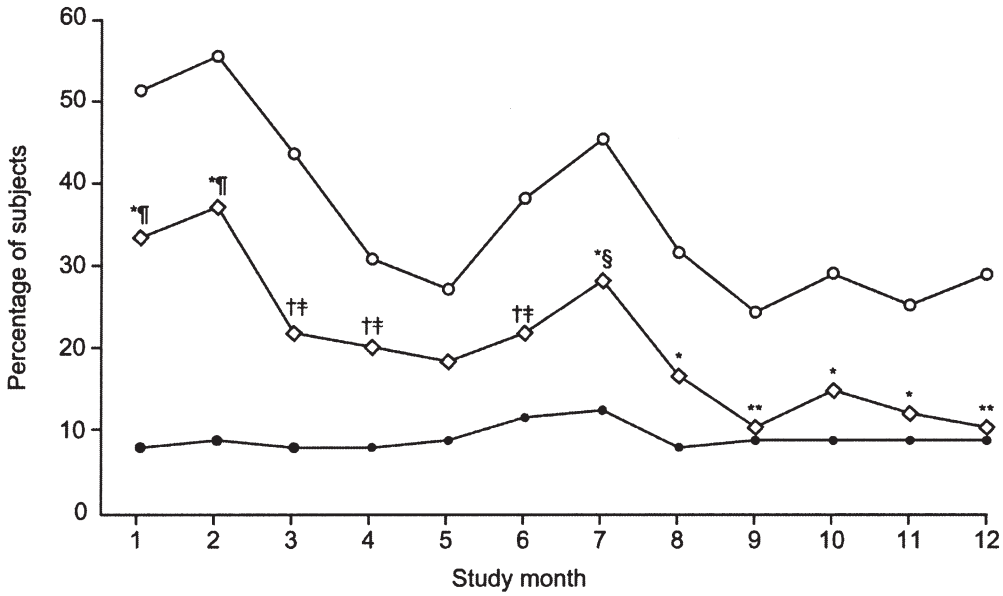

Fig 3. Percentage of subjects with bleeding and/or spotting, intent-to-threat/last observation carried forward population. The *asterisk* denotes $P < .05$; the *double asterisk* denotes $P < .01$; the *dagger* denotes $P < .001$, compared with CEE/MPA; the *double dagger* denotes $P < .05$; the *double S* denotes $P < .01$; the *paragraph symbol* denotes $P < .001$, compared with placebo. The data are based on Cochran-Mantel-Haenszel (general association) test stratified by center. The *closed circles* represent placebo; the *open diamonds* represent 1/5 NA/EE; and the *open circles* represent CEE/MPA.

Table II. Comparative analyses of bleeding profiles at month 3 for the intent-to-treat/last observation carried forward population

	Placebo (n = 117)	*1/5 NA/EE (n = 121)*	*CEE/MPA (n = 119)*	*P value (1/5 NA/EE vs CEE/MPA)*	*P value (1/5 NA/EE vs placebo)*
Bleeding incidence (%)	3	12	23	.029	.024
Bleeding and/or spotting incidence (%)	8	22	44	<.001	.023
Duration of bleeding (d)*	0.1 ± 0.05	0.5 ± 0.17	1.2 ± 0.26	.004	Not calculated
Duration of bleeding and/or spotting (d)*	0.4 ± 0.20	1.7 ± 0.42	4.1 ± 0.63	<.001	.056

*Data are given as mean ± SEM.

12 was statistically indistinguishable from that in placebo group (Fig 4).

Cumulative amenorrhea. The incidence of cumulative amenorrhea in the 1/5 NA/EE group was significantly greater than that in the CEE/MPA group at every monthly interval ($P < .05$; Fig 5). In addition, the incidence of cumulative amenorrhea in the 1/5 NA/EE group was statistically indistinguishable from that in placebo-treated subjects at month 9 through the end of the study.

Safety assessments. No deaths were reported during the study. Overall, the proportions of subjects who reported adverse events and treatment-associated adverse events were similar across the placebo, 1/5 NA/EE, and CEE/MPA groups (Table III). Many of the treatment-associated adverse events were typical of hormone therapy (eg, headache [occurred in 5% of the 1/5 NA/EE group and 4% of the CEE/MPA group] and breast pain [reported in 5% of the 1/5 NA/EE group and 8% of the CEE/MPA group]). Most treatment-associated adverse events were of mild-to-moderate intensity.

During the study, 7 subjects across all 3 treatment groups reported 9 serious adverse events. Of these, 1 subject was in the placebo group; 2 subjects were in the 1/5 NA/EE group, and 4 subjects were in the CEE/MPA group. One patient in the CEE/MPA group experienced a serious adverse event that the investigator judged to be possibly related to the study treatment. This adverse event was breast cancer. The subject was 48 years old and white and was diagnosed with a well-differentiated, infiltrating ductal cell carcinoma at 95 days after the study completion. All other serious adverse events were either unlikely to be or definitely not related to treatment.

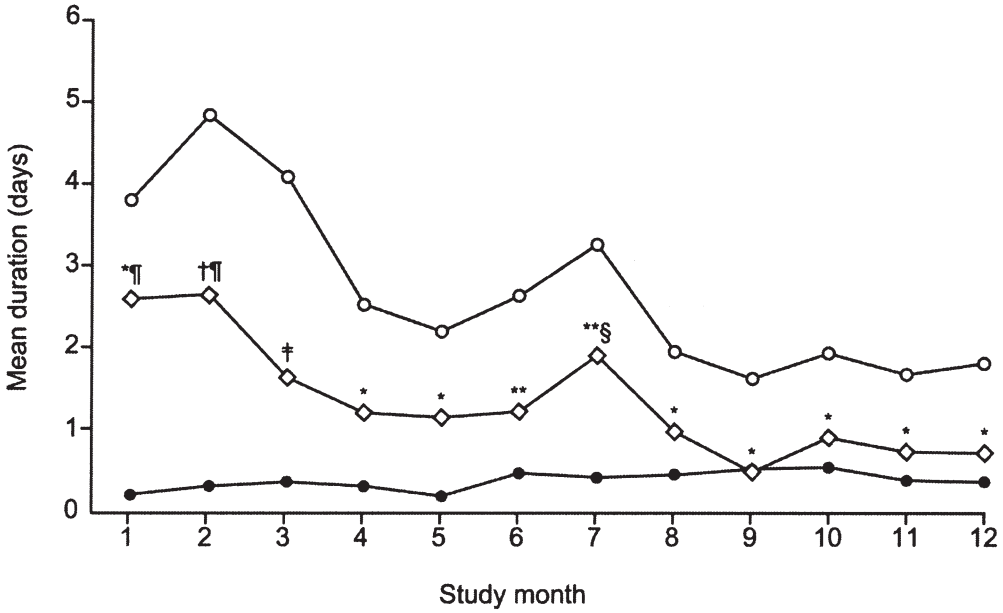

Fig 4. Mean duration (days) of bleeding and/or spotting, intent-to-threat/last observation carried forward population. The *asterisk* denotes $P \leq .05$; the *double asterisk* denotes $P < .01$; the *dagger* denotes $P < .001$, compared with CEE/MPA; the *double dagger* denotes $P < .05$; the *double S* denotes $P < .01$; the *paragraph symbol* denotes $P < .001$, compared with placebo. Based on an analysis of variance model with factors for treatment group and center. The *closed circles* represent placebo; the *open diamonds* represent 1/5 NA/EE; and the *open circles* represent CEE/MPA.

Table III. Overview of adverse events

	Placebo (n = 117)	*1/5 NA/EE (n = 121)*	*CEE/MPA (n = 119)*
Subjects with adverse events (No.)			
All adverse events	88 (75%)	96 (79%)	93 (78%)
Treatment-associated adverse events	33 (28%)	45 (37%)	41 (34%)
Incidence of adverse events associated with treatment (No.)			
Headache	11 (9%)	6 (5%)	5 (4%)
Breast pain	4 (3%)	6 (5%)	10 (8%)
Uterine fibroid tumor	1 (<1%)	3 (2%)	4 (3%)
Abdominal pain	4 (3%)	2 (2%)	3 (3%)
Flatulence	3 (3%)	4 (3%)	9 (8%)
Nausea and/or vomiting	2 (2%)	1 (<1%)	2 (2%)
Vasodilation	9 (8%)	5 (4%)	1 (<1%)
Myalgia	1 (<1%)	6 (5%)	0
Subjects with serious adverse events (No.)			
All adverse events	1 (<1%)	2 (2%)	4 (3%)
Treatment-associated adverse events	0	0	1 (<1%)
Withdrawals because of adverse events (No.)			
All adverse events	9 (8%)	13 (11%)	16 (13%)
Treatment-associated adverse events	6 (5%)	11 (9%)	9 (8%)

One subject in the CEE/MPA group experienced a thromboembolic-type event, but this was not serious. The subject, who was 48 years old and white with a history of light smoking (2 cigarettes per day) and a self-described heavy exerciser reported right-side numbness on 3 occasions, which was considered to be associated with the study medication, and consequently withdrew prematurely from the study on day 252. No subjects in the 1/5 NA/EE or placebo groups reported thromboembolic-type events.

Twenty-seven percent of the 1/5 NA/EE group, 29% of the CEE/MPA group, and 26% of the placebo group withdrew from the study. For the 1/5 NA/EE group, withdrawal occurred because of adverse events (11%), other/administrative reasons (14%), and lack of compliance (2%). Study withdrawal in the CEE/MPA group was attributed to adverse events (13%), other/administrative reasons (12%), lack of compliance (3%), and lack of efficacy (<1%). These rates were not statistically different between active treatments.

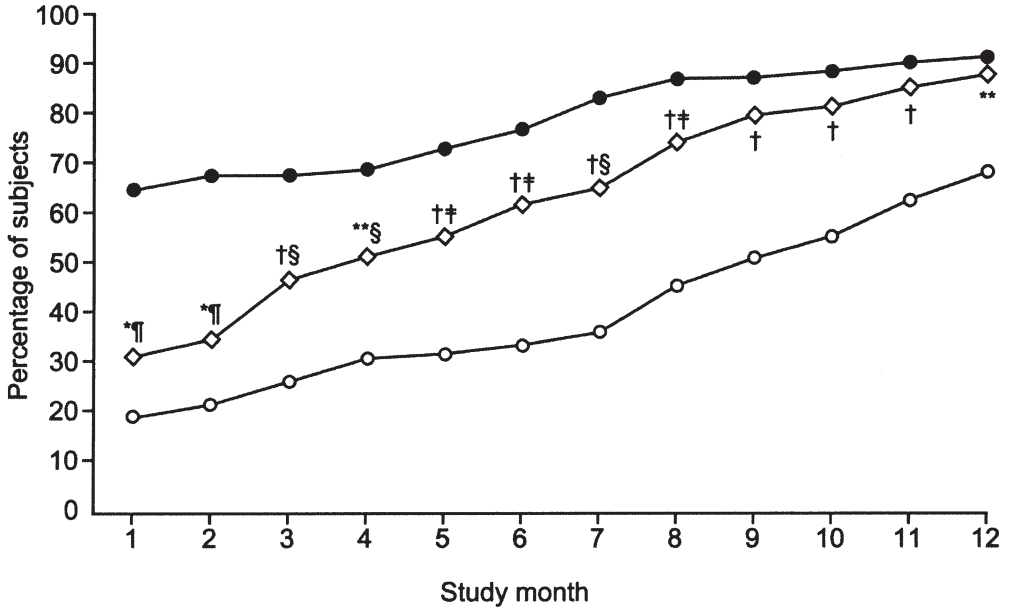

Fig 5. Incidence of cumulative amenorrhea, intent-to-threat/last observation carried forward population. The *asterisk* denotes $P < .05$; the *double asterisk* denotes $P < .01$; the *dagger* denotes $P \leq .001$, compared with CEE/MPA; the *double dagger* denotes $P < .05$; the *double S* denotes $P < .01$; the *paragraph symbol* denotes $P < .001$, compared with placebo. The data are based on Cochran-Mantel-Haenszel (general association) test stratified by center. The *closed circles* represent placebo; the *open diamonds* represent 1/5 NA/EE; and the *open circles* represent CEE/MPA.

Changes in laboratory parameters in all treatment groups were minor and were not considered to be clinically significant.

Comment

The current study provides a direct comparison of the effects of 2 commercially available CCHRT regimens, 1/5 NA/EE and CEE/MPA, on bleeding in postmenopausal women. For all measures that pertain to bleeding control, including incidence of amenorrhea, vaginal bleeding and/or spotting, mean duration of bleeding and bleeding and/or spotting, and cumulative amenorrhea, 1/5 NA/EE was significantly better than CEE/MPA. The measurement of cumulative amenorrhea, as defined and used in this study, is the most rigorous method for the assessment of permanent absence of bleeding and spotting, as it reflects the percentage of patients who achieve amenorrhea that persists for the duration of the study. The incidence of cumulative amenorrhea was significantly greater among the 1/5 NA/EE group than among the CEE/MPA group at every monthly interval. Moreover, by months 9 through 12, the incidence of cumulative amenorrhea among the 1/5 NA/EE group members was not significantly different from that among placebo-treated subjects.

Reported incidences of vaginal bleeding that were associated with various CCHRTs differ widely, possibly owing to of varying definitions of vaginal bleeding, spotting and amenorrhea/bleeding incidence, or differences in the populations or time points studied. For example, Archer et al[15] described the incidence of bleeding among patients who received 0.625 mg CEE combined with either 2.5 or 5.0 mg MPA as the percentage of all evaluable cycles in which amenorrhea was interrupted. Amenorrhea was defined as the absence of any bleeding or spotting during the entire 28-day treatment cycle. Incidences of bleeding at cycle 13, according to this method, were 38.6% and 27.2% among patients who were assigned randomly to 2.5 and 5.0 mg MPA, respectively.[15] Weinstein et al[19] also investigated the incidence of bleeding in patients who received CEE (0.625 mg)/MPA (2.5 or 5.0 mg), over a 1-year period (n = 92). In contrast to the study by Archer et al,[15] a 65% incidence rate was observed over the entire study period for all patients who were enrolled. These 2 studies clearly demonstrate the need for standardized comparisons in clinical trials, to allow meaningful comparison of the bleeding profiles of different HRT products.

One of the strengths of this study is that it prospectively assessed an array of bleeding parameters according to rigorous definitions. In addition, and in contrast to a number of studies of other CCHRTs that reported low rates of vaginal bleeding, a comparative control was included. Thus, the findings of good control of vaginal bleeding with 1/5 NA/EE that are reported in this present study can be considered reliable. A potential weakness, however, is that the CEE/MPA control arm was open-label. Nevertheless, the cumulative amenorrhea data that were obtained for

CEE/MPA in this study are quite similar to those reported in the prescribing information for this product.[21]

The continuous use of NA in combination with EE has been shown to prevent excessive endometrial proliferation,[21] minimize vaginal bleeding, provide relief from vasomotor symptoms,[22] and increase bone mineral density (data on file, Pfizer Global Research and Development, 2002). Symons et al[17] recently reported short-term data that related to the effect of various dose combinations of NA and EE on vaginal bleeding, as assessed in 2 randomized, placebo-controlled clinical trials of 12- and 16-week duration. In both trials, significant decreases in vaginal bleeding and spotting were achieved in a relatively short time.

The mechanisms by which exogenous estrogen/progestin regimens exert their effects on vaginal bleeding are unknown. One putative mechanism is through the potential stimulatory effect of progestins on endometrial vascular endothelial growth factor, which could result in inappropriate angiogenesis.[23] The balance between estrogen and progestin doses[24] and the different characteristics of progestin types[25] may also be important factors. Nevertheless, it has been established that the continuous combined administration of NA/EE at the doses used in the study described in the current report does not result in endometrial hyperplasia or significant proliferation.[22] Moreover, the addition of 1 mg NA to 5 μg EE has been shown to significantly reduce the incidence of endometrial proliferation at 12 months compared with unopposed EE at the same dosage (data on file, Pfizer Global Research and Development, 2002).

This randomized clinical trial was the first long-term comparison of the vaginal bleeding profiles of 2 CCHRT regimens. The findings demonstrate a superior bleeding profile for continuous combined therapy that consists of 1 mg NA/5 μg EE relative to the regimen comprising 0.625 mg CEE/2.5 mg MPA. The difference in bleeding profiles was evident for all measures that were obtained in this study. The increased percentage of postmenopausal women who achieve and maintain amenorrhea with 1/5 NA/EE may result in improved long-term treatment adherence and associated health benefits.

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