

Effect of Lower Doses of Conjugated Equine Estrogens With and Without Medroxyprogesterone Acetate on Bone in Early Postmenopausal Women

Robert Lindsay, MBChB, PhD, FRCP

J. Christopher Gallagher, MD

Michael Kleerekoper, MD

James H. Pickar, MD

THE USE OF LOWER DOSES OF ESTROGENS for hormone replacement therapy (HRT; estrogen in combination with a progestin) in postmenopausal women has been proposed to enhance the initiation and long-term continuation of HRT.^{1,2} Long-term continuation is especially important for preventing the loss of bone mineral density (BMD),¹ a factor cited by a large percentage of patients as influencing their decision making regarding HRT.³

A small number of low-dose estrogen formulations have been approved in the United States for preventing menopausal symptoms or osteoporosis: oral conjugated equine estrogens (CEEs) or esterified estrogens at 0.3 mg/d; oral micronized estradiol at 0.5 mg/d; and transdermal 17 β -estradiol at 0.025 mg/d. Genant et al⁴ demonstrated that esterified estrogens at 0.3 mg/d for 24 months, combined with a calcium supplement, increased BMD compared with baseline and placebo. However, the Continuous Hormones as Replacement Therapy (CHART) Study³ found that doses of ethinyl estradiol (<5 μ g/d) and continuous norethindrone acetate (1 mg/d) combined with calcium supplementation did not significantly increase BMD from baseline

Context Lower-than-commonly-prescribed doses of conjugated equine estrogens (CEEs) with medroxyprogesterone acetate (MPA) improve vasomotor symptoms and vaginal atrophy, provide acceptable bleeding and lipid profiles, and afford endometrial protection. This lower-dose therapy's protection against loss of bone mineral density (BMD) associated with menopause has not been thoroughly investigated.

Objective To determine the effects of lower doses of CEEs only or CEEs-MPA on spine and hip BMD, total body bone mineral content (BMC), and biochemical markers of bone turnover in postmenopausal women.

Design and Setting Two-year randomized, double-blind, placebo-controlled substudy of the Women's Health, Osteoporosis, Progestin, Estrogen trial, conducted at 19 US centers between August 1995 and October 2000.

Participants Eight hundred twenty-two healthy postmenopausal women aged 40 to 65 years who were within 4 years of their last menstrual period.

Interventions Patients were randomly assigned to receive CEEs, 0.625; CEEs, 0.625 and MPA, 2.5; CEEs, 0.45; CEEs, 0.45 and MPA, 2.5; CEEs, 0.45 and MPA, 1.5; CEEs, 0.3; CEEs 0.3 and MPA, 1.5 (all doses in mg/d); or placebo for 2 years. All participants also received elemental calcium at 600 mg/d.

Main Outcome Measures Changes from baseline in spine and total hip BMD, total body BMC, and biochemical markers of bone turnover (serum osteocalcin and urinary cross-linked *N*-telopeptides of type I collagen), assessed at 6-month intervals and compared among treatment groups with a modified intention-to-treat approach.

Results At 24 months, women assigned to all of the active treatment groups had significant gains from baseline ($P < .001$) in spine and hip BMD and total body BMC (except total body BMC in the group receiving CEEs, 0.3 mg/d). These changes were significantly different from those in the placebo group, in which losses of bone mass in spine and total body were evident over the course of the study ($P < .001$). The loss in hip BMD from baseline in the placebo group was significant at 18 ($P = .02$) but not at 24 months ($P = .06$). Osteocalcin and *N*-telopeptides of type I collagen were significantly reduced from baseline ($P < .001$) for all active treatment groups at all time points; no changes were found for the placebo group. For women treated with CEEs alone, the gains in spine BMD for the group taking CEEs, 0.625 mg/d, were significantly higher than those of the group taking CEEs, 0.3 mg/d ($P = .02$), but not the group treated with CEEs, 0.45 mg/d ($P = .48$).

Conclusions Doses of CEEs or CEEs-MPA lower than 0.625 mg/d effectively increase BMD and BMC in early postmenopausal women.

JAMA. 2002;287:2668-2676

www.jama.com

Author Affiliations are listed at the end of this article.
Corresponding Author: Michael Kleerekoper, MD, Division of Endocrinology, Wayne State University School of Medicine, University Health Center, 4201 St Antoine, Suite 4H, Detroit, MI 48201 (e-mail: Mkleerekoper@intmed.wayne.edu).

Reprints: Robert Lindsay, MBChB, PhD, FRCP, Internal Medicine, Helen Hayes Hospital, Rte 9W, West Haverstraw, NY 10993 (e-mail: lindsayr@helenhayeshosp.org).

after 2 years. A small randomized trial⁶ in older (>65 years of age) postmenopausal women with low BMD found BMD increases with CEEs (0.3 mg/d) and continuous medroxyprogesterone acetate (MPA) (2.5 mg/d) throughout a 3.5-year period when combined with 25-hydroxyvitamin D and adequate calcium intake. Using this same HRT formulation combined only with calcium supplements, Gambacciani et al⁷ recently reported greater BMD gains in women who received the combination than in women who received calcium alone.

In a number of clinical trials using commonly prescribed doses, estrogen replacement therapy (ERT) or HRT has been shown to reduce the incidence of vertebral and nonvertebral fractures, in large part by reversing the loss of BMD.⁸⁻¹⁰ Commonly prescribed doses of CEEs (0.625 mg/d) have been shown to maintain or increase BMD in postmenopausal women¹¹⁻¹⁶; however, the dose-response relationship for the maintenance of BMD with CEEs is not well understood. Only 2 small studies published in the early 1980s systematically evaluated the effects of CEEs on bone across different doses. Both of these studies suggested that CEE doses less than 0.625 mg/d were not completely effective in reducing bone loss.^{11,12} However, these studies were conducted in women, many of whom had undergone surgical menopause, and one study used technologies to assess changes in bone that are not commonly used today. In addition, neither study evaluated the effects of CEEs on hip BMD, the most important site for osteoporosis-related fractures.¹⁷

In the United States, postmenopausal women who have an intact uterus and are given CEEs also receive the progestin MPA for endometrial protection. The bone-preserving effect of 0.625 mg of CEEs combined continuously with 2.5 mg of MPA has been established^{14,16}; however, in these studies MPA did not induce an added benefit compared with CEEs alone. The addition of MPA (10 mg/d) to 0.3 mg of CEEs resulted in preservation of bone

density in the spine that was similar to that seen with 0.625 mg of CEEs alone,¹³ suggesting that MPA may produce an added benefit when combined with lower CEE doses. A dose-response relationship for the impact of CEEs-MPA on BMD has not been investigated.

The purpose of this substudy was to evaluate the efficacy of lower doses of CEEs alone and CEEs-MPA on bone mass and biochemical markers of bone turnover in the large, multicenter, placebo-controlled randomized Women's Health, Osteoporosis, Progestin, Estrogen (Women's HOPE) trial. In addition, the use of multiple doses of CEEs alone and CEEs-MPA allowed us to revisit the dose-response relationship between CEEs and BMD changes by using current technologies, as well as to evaluate the dose-response relationship between CEEs-MPA and BMD.

METHODS

Participants

Healthy postmenopausal women aged 40 to 65 years were recruited for the 2-year substudy of the Women's HOPE trial that was conducted between August 1995 and October 2000. Women were eligible if they had an intact uterus, no menses within the last year, follicle-stimulating hormone levels of at least 30 mIU/mL, 17 β -estradiol levels of no more than 50 pg/mL (184 pmol/L), were within 4 years of their last menses, and were within 20% of their normal weight range. Exclusion criteria included any disorders that affect bone metabolism, clinically important degenerative changes in the lumbar spine that may interfere with dual-energy x-ray absorptiometry (DXA) (eg, spinal fusion), significant scoliosis according to DXA, at least 2 abnormal lumbar vertebrae from L1 to L4, and lumbar spine baseline BMD measurement more than 3 SDs below the mean for healthy young women. In addition, women were excluded if they smoked more than 15 cigarettes daily, had taken calcitonin within the past 6 months, and had ever used bisphosphonates or fluoride for more than 1 year or used fluo-

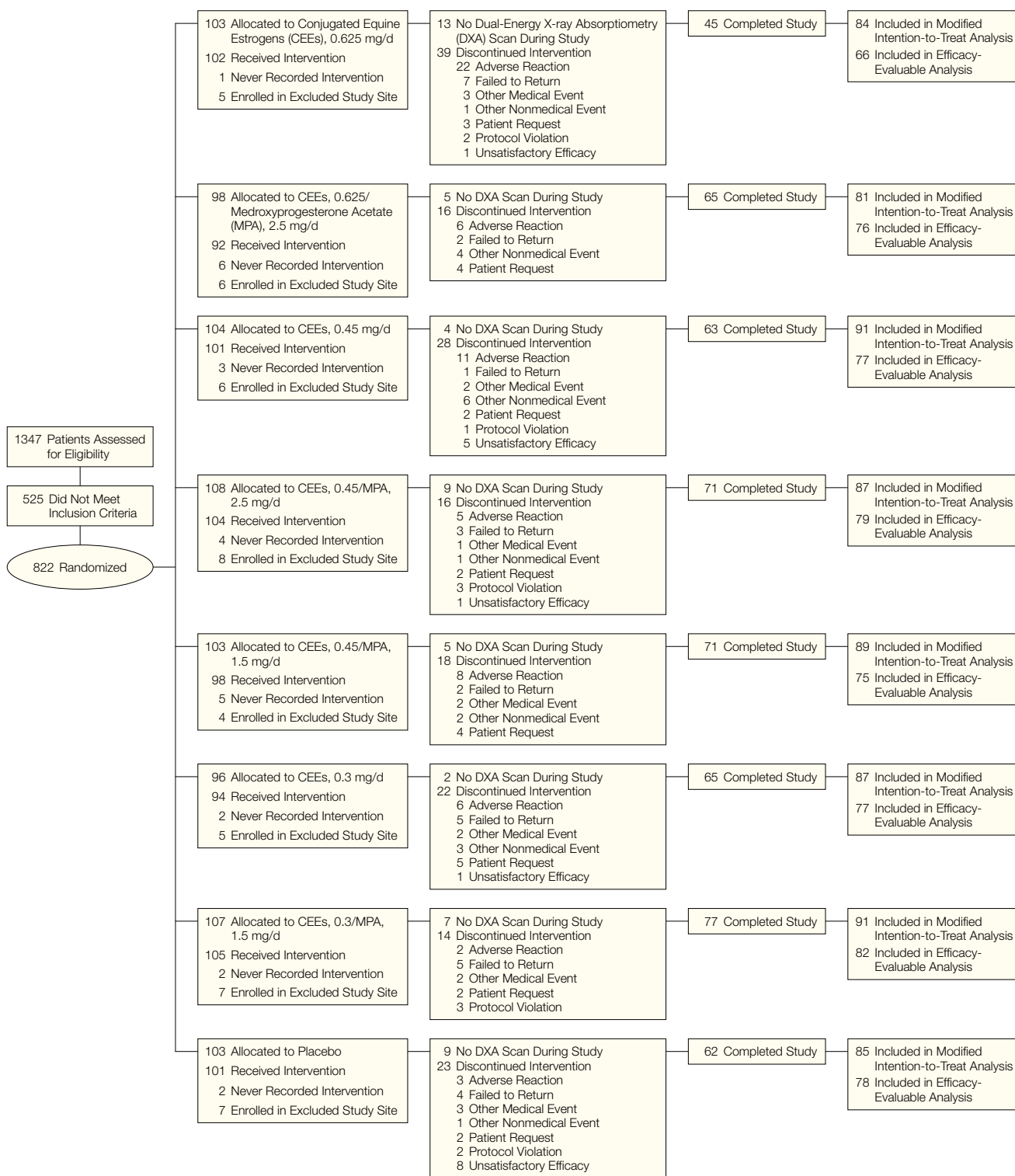
ride within the past year. The use of medication containing estrogens, progestins, or androgens within 12 weeks of the prestudy screening, a known hypersensitivity to estrogens or progestins, the documentation of endometrial hyperplasia, or an abnormal Papanicolaou test result also resulted in exclusion from the study.

Complete details of the 2-year Women's HOPE trial, including substudy sites¹⁸ and the first-year lipid data from this substudy,¹⁹ have been reported. The institutional review board at each of the 19 substudy sites approved all procedures, and each subject provided written informed consent before enrollment.

Study Design

Following screening, 822 women were randomized to 1 of 8 treatment groups: CEEs at 0.625 mg/d; CEEs at 0.625 mg/d and MPA at 2.5 mg/d; CEEs at 0.45 mg/d; CEEs at 0.45 mg/d and MPA at 2.5 mg/d; CEEs at 0.45 mg/d and MPA at 1.5 mg/d; CEEs at 0.3 mg/d; CEEs at 0.3 mg/d and MPA at 1.5 mg/d; and placebo (FIGURE 1). A computer-generated randomization table was used for assignment to the treatment groups. The randomization table used for treatment group assignment was produced with an SAS-based computerized randomization program (PROC PLAN, version 6; SAS Institute, Cary, NC). The randomization was done in blocks of 16. Each block contained 2 randomization numbers for each of the 8 treatment groups. Randomization numbers were issued to the investigational sites in blocks of 16. Because the CEEs and the CEEs-MPA tablets were different sizes, 2 placebos were necessary to mask the treatments; therefore, a double-dummy (ie, dual-placebo) double-blind design was used. Subjects were instructed to take 1 tablet of CEEs or matching placebo and 1 tablet of CEEs-MPA or matching placebo. Participants also received 1 calcium carbonate supplement daily (600 mg of elemental calcium per tablet [Caltrate; Whitehall-Robins, Madison, NJ]). All tablets were taken orally once daily

Figure 1. Flow of Participants Through the Trial



The disposition of the patients enrolled in the 2-year Women’s Health, Osteoporosis, Progestin, Estrogen trial substudy are shown for all groups in both modified intention-to-treat and efficacy-evaluable populations.

at approximately the same time each day. Treatment compliance was assessed by monitoring daily diary cards.

Measurements

Bone Mineral Density and Bone Mineral Content. Bone mineral density of the anteroposterior lumbar spine (L2 to L4) and total hip as well as total body bone mineral content (BMC) were assessed by DXA with DPX-L scanners (Lunar Corp, Madison, Wis). Baseline measurements were obtained on 2 occasions no more than 3 weeks apart. If the 2 prestudy scan values differed by more than 5%, a third pretreatment scan was performed before randomization. The findings of the 3 scans were compared; the 2 scans closest to the mean of the 3 and within 5% of each other were recorded.

Following randomization, BMD and BMC were assessed every 6 months for 2 years, with replicate measurements made at the final visit. Scans were centrally analyzed and reviewed at the Bone Quality Control Center (Helen Hayes Hospital, West Haverstraw, NY). Quality-control procedures included cross-calibration with the European Spine Phantom (QRM, Moehrendorf, Germany) and longitudinal tracking of scanner performance with the Lunar Spine Phantom (Lunar Corp, Madison, Wis). If annualized bone loss was more than 7.5% from baseline for spine BMD, the patient was given the option to withdraw. Two women in the placebo group withdrew for this reason.

Biochemical Markers of Bone Turnover. After an overnight fast, blood for the determination of serum osteocalcin, a marker of bone formation, and urine (second void) for the determination of cross-linked *N*-telopeptides of type I collagen, a marker of bone resorption, were collected at individual clinical sites during the prestudy screening and at each 6-month visit. Analyses were performed by the Core Laboratory for Clinical Studies of Washington University (St Louis, Mo).

The concentration of intact osteocalcin and *N*-telopeptides of type I collagen was determined with commer-

cially available, enzyme-linked immunosorbent assay (ELISA) kits. All samples from a given patient were assayed on the same ELISA plate. The intra-assay coefficient of variation was less than 6% for osteocalcin and less than 9.5% for *N*-telopeptides of type I collagen. Urinary creatinine concentration was measured using a commercially available kit on a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, Ind). The intra-assay coefficient of variation was less than 3%.

Statistical Analyses

All women who were randomized to treatment, recorded taking at least 1 dose of the study drug, and received at least 1 BMD measurement postbaseline were included in the modified intention-to-treat (MITT) analyses. The last-observation-carried-forward procedure was used for women who did not complete the study. Thus, if a subject discontinued participation, the data from her last measured response were carried forward to all subsequent scheduled observations and included in the analysis. This procedure prevented the bias that would have resulted from subjective decisions about missing data. We also analyzed the BMD and BMC data in an efficacy-evaluable population to determine the true effect of CEEs or CEEs-MPA on women who complied with the study protocol. For this study, the efficacy-evaluable population included women who had at least 1 prestudy BMD measurement and at least 2 measurements during the study with no more than 1 of these being at the termination visit(s), had reported taking 80% of their study medication, and were not using unacceptable concomitant medications. For women in the efficacy-evaluable population who met the criteria but discontinued the study before its conclusion, the last-observation-carried-forward procedure was also used.

Baseline characteristics were compared between groups by using a 1-way analysis of variance procedure; a χ^2 analysis was used for categorical variables (SAS, version 6.12; SAS Institute, Cary, NC). The changes in percentage

from baseline for spine and hip BMD and total body BMC were analyzed by analysis of covariance, with time since menopause, body weight, and baseline bone mass included as covariates. Median changes in percentage from baseline were analyzed for urinary *N*-telopeptides of type I collagen and serum osteocalcin by using nonparametric methods (signed rank test). Both treatment and investigational site were included as factors in the analyses. The least significant difference procedure was used for pairwise comparisons. Product moment correlation coefficients were calculated to assess the relationship between changes in BMD and BMC measures and the relationship between changes in biochemical markers and changes in BMD or BMC. Statistical significance was set a priori at $P < .05$. Data are presented as mean (SEM) unless otherwise noted.

RESULTS

Subjects

The disposition of the subjects enrolled in the 2-year substudy is shown in Figure 1. Of the 822 women randomized to treatment, 48 were excluded because of a study site violation and 25 never received treatment. In addition, 54 women either did not record taking 1 dose of the study drug or did not meet the criteria for BMD assessment established for the MITT population. The TABLE presents the baseline characteristics of the 695 subjects in the MITT population; there were no differences among groups. Eighty-five patients in the MITT population did not meet the criteria for inclusion in the efficacy-evaluable population; thus, 610 were included in the efficacy-evaluable population. The baseline characteristics for the efficacy-evaluable population were similar (data not shown).

Measures of BMD and BMC

The MITT and efficacy-evaluable data for all BMD sites and BMC are reported. The significant differences noted between the active treatment group and the placebo group for these measures were also observed in all patients who

were randomized to treatment, including those who dropped out before having any BMD data beyond the baseline visit (pure ITT analysis). Because the MITT and efficacy-evaluable analyses were the primary analyses in the protocol for this trial, only these results are presented.

For both populations, adjusted mean changes in percentage from baseline in spine BMD for the CEEs alone and the CEEs-MPA groups over time are displayed in FIGURE 2. By the 24-month visit, women assigned to all of the active treatment groups had significant gains ($P < .001$) in spine BMD. In contrast, women in the placebo group had a significant loss of spine BMD ($P < .001$). At all time points, the gains from baseline for all active treatment groups were significantly different ($P < .001$) from the loss observed in the placebo group.

When the changes from baseline in spine BMD were compared among the 3 groups treated with CEEs alone for the MITT population, only the difference between the groups taking CEEs at 0.625 mg/d and those taking CEEs at 0.3 mg/d (2.43% [SEM, 0.35%] vs 1.33% [0.34%]) was significant ($P = .02$). Adding MPA to CEEs significantly increased spine BMD relative to

CEEs alone at 2 years for the higher CEE doses. The gain for the group taking CEEs at 0.625 mg/d and MPA at 2.5 mg/d was significantly greater than that observed for the group taking CEEs at 0.625 mg/d (3.46% [0.35%] vs 2.43% [0.35%]; $P = .03$). The difference between the gain in spine BMD at 24 months for the group taking CEEs at 0.45 mg/d and MPA at 2.5 mg/d (3.01% [0.34%]) and the group taking CEEs at 0.45 mg/d (2.09% [0.33%]) was also statistically significant ($P = .05$). In contrast, the increase in spine BMD for the group taking CEEs at 0.45 mg/d and MPA at 1.5 mg/d (2.22% [0.33%]) was not different from the gains observed for either the group taking CEEs at 0.45 mg/d and MPA at 2.5 mg/d or the group taking CEEs at 0.45 mg/d. The addition of 1.5 mg of MPA to 0.3 mg of CEEs resulted in changes in spine BMD that were numerically greater than those seen with CEEs alone (Figure 2); however, these values were not significantly different.

The changes from baseline in total hip BMD over time are presented in FIGURE 3 for years 1 and 2 for both the MITT and efficacy-evaluable populations. Significant increases from baseline ($P < .05$) were observed for all active treatment groups at all time points.

At 24 months, the gains in hip BMD from baseline for all active treatment groups were significantly greater than for placebo ($P < .001$). At 18 months, the placebo group lost hip BMD ($P = .02$ for MITT and $P = .01$ for efficacy-evaluable population); however, the loss in hip BMD at 24 months was not statistically different from baseline ($P = .06$) for the MITT population. There were no significant differences between CEEs in combination with MPA and the comparable dose of CEEs alone at 24 months, nor were there differences in the gains in hip BMD among any of the groups taking CEEs only.

The gains in total body BMC at 2 years for the MITT population were significant ($P \leq .001$) for all of the active treatment groups, except those taking CEEs at 0.3 mg/d. Increases (SEM) ranged from 1.03% (0.34%) in the group taking CEEs at 0.625 mg/d to 1.74% (0.33%) in the group taking CEEs at 0.45 mg/d and MPA at 2.5 mg/d. In contrast, women in the placebo group had experienced significant ($P < .001$) loss from baseline in total BMC (-2.39% [0.33%]) by 24 months. This loss was significantly ($P < .001$) different from that in all of the active treatment groups at each time point. As noted for hip BMD, the ad-

Table. Baseline Characteristics for the Modified Intention-to-Treat Population in the Women's HOPE Substudy by Treatment Group*

Characteristic	CEEs, 0.625 mg/d (n = 84)	CEEs, 0.625 and MPA, 2.5 mg/d (n = 81)	CEEs, 0.45 mg/d (n = 91)	CEEs, 0.45 and MPA, 2.5 mg/d (n = 87)	CEEs, 0.45 and MPA, 1.5 mg/d (n = 89)	CEEs, 0.3 mg/d (n = 87)	CEEs, 0.3 and MPA, 1.5 mg/d (n = 91)	Placebo (n = 85)	Total (N = 695)
Age, y	52.1 (3.1)	51.5 (4.2)	51.9 (3.6)	51.6 (3.9)	51.1 (3.5)	52.2 (3.9)	51.4 (3.5)	51.4 (4.0)	51.6 (3.7)
Height, cm	164.5 (5.1)	164.3 (6.3)	164.3 (6.6)	163.8 (6.6)	165.3 (6.0)	162.5 (5.8)	163.5 (6.2)	163.2 (5.6)	163.9 (6.1)
Weight, kg	67.4 (8.4)	66.2 (8.8)	65.6 (8.6)	65.1 (9.0)	67.2 (9.2)	64.6 (8.0)	64.7 (8.2)	64.8 (9.0)	65.7 (8.7)
Body mass index, kg/m ²	24.9 (2.7)	24.5 (2.7)	24.3 (2.7)	24.2 (2.7)	24.6 (2.9)	24.5 (2.7)	24.2 (2.8)	24.3 (3.0)	24.4 (2.8)
Age at menopause, y	49.8 (3.0)	49.3 (4.2)	49.3 (3.4)	49.2 (3.7)	48.8 (3.3)	49.9 (3.6)	49.0 (3.4)	49.0 (3.8)	49.3 (3.6)
Years since menopause	2.3 (0.9)	2.2 (0.9)	2.5 (1.0)	2.5 (0.9)	2.3 (0.9)	2.3 (1.0)	2.3 (1.0)	2.3 (1.0)	2.3 (0.9)
Parity, No.	2.9 (1.8)	2.6 (1.6)	2.8 (1.8)	2.8 (1.8)	2.8 (2.1)	2.9 (1.8)	3.0 (1.7)	2.6 (1.7)	2.8 (1.8)
Ethnicity, %†									
White	92	90	89	98	97	90	88	94	92
Other	8	9	10	2	3	10	12	5	8
Spine BMD, g/cm ²	1.174 (0.153)	1.144 (0.164)	1.135 (0.155)	1.152 (0.171)	1.158 (0.141)	1.140 (0.150)	1.139 (0.145)	1.144 (0.144)	1.148 (0.153)
Total hip BMD, g/cm ²	0.979 (0.136)	0.965 (0.144)	0.954 (0.136)	0.956 (0.147)	0.948 (0.130)	0.942 (0.121)	0.944 (0.122)	0.944 (0.137)	0.953 (0.134)
Total body BMC, g	2366 (298)	2343 (311)	2326 (318)	2307 (347)	2373 (272)	2286 (264)	2299 (306)	2292 (283)	2324 (301)

*Values are presented as mean (SD). HOPE indicates Women's Health, Osteoporosis, Progestin, Estrogen trial; CEEs, conjugated equine estrogens; MPA, medroxyprogesterone acetate; BMD, bone mineral density; and BMC, bone mineral content. $P > .05$ for all between-group comparisons.

†Percentages may not add to 100 because of rounding.

dition of MPA to CEEs did not significantly influence the total body BMC response, nor was there a significant dose-response effect for CEEs alone.

Biochemical Markers of Bone Turnover

The median values for change in percentage from baseline in the MITT population are shown for *N*-telopeptides of type I collagen (FIGURE 4A) and osteocalcin (Figure 4B). For all active treatment groups, *N*-telopeptides of type I collagen and osteocalcin were significantly ($P < .001$) reduced from baseline at all time points. By 2 years, reductions in *N*-telopeptides of type I collagen ranged from 55.0% for the group taking CEEs at 0.625 mg/d and MPA at 2.5 mg/d to 34.0% for the group taking CEEs at 0.3 mg/d and MPA at 1.5 mg/d. The decrease in serum osteocalcin ranged from 36.6% for CEEs at 0.625 mg/d and MPA at 2.5 mg/d to 22.1% with CEEs at 0.3 mg/d. The reduction in both bone markers was smaller ($P < .05$) for the women in the groups taking CEEs at 0.3 mg/d and CEEs at 0.3 mg/d and MPA at 1.5 mg/d than in the groups taking higher doses. In contrast to the active treatment groups, the placebo group showed no changes for either biochemical marker of bone turnover. The decline in *N*-telopeptides of type I collagen and osteocalcin occurred primarily within the first 6 months of treatment, with relatively little additional change thereafter for all CEEs-only and CEEs-MPA doses.

Adverse Events

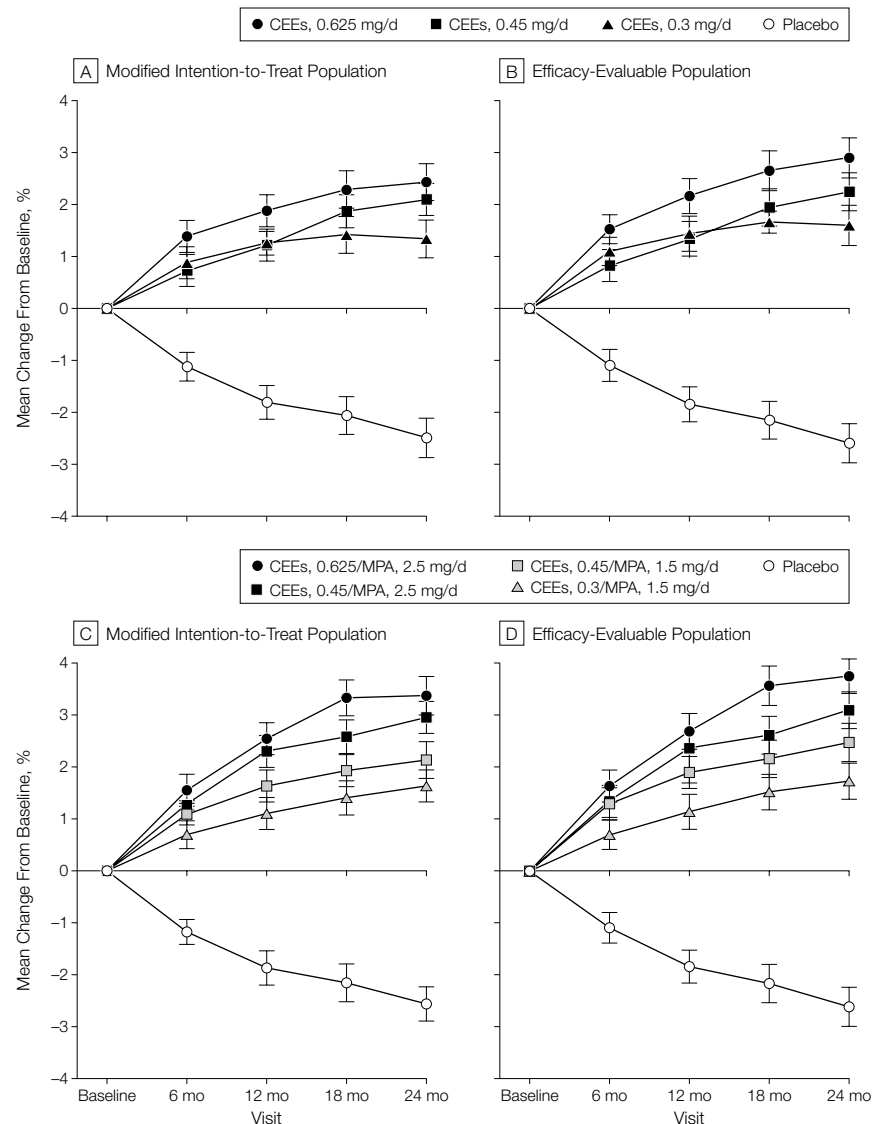
During the 2-year study, treatment-emergent adverse events were reported by 93% of subjects in the placebo group and 96% of those in the active treatment groups. The incidence of adverse events that were reported by at least 5% of patients in any one group and that were significantly different in the active treatment groups compared with placebo is summarized below.

Endometrial hyperplasia, metrorrhagia, and vaginal bleeding were re-

ported more frequently in the CEEs-only treatment groups compared with placebo ($P < .05$). The incidence of breast pain and vaginal bleeding was higher ($P < .05$) in the CEEs-MPA treatment groups vs placebo. In contrast, vaginal dryness was significantly greater ($P < .05$) in the placebo group compared with that in either the CEEs-

only or CEEs-MPA group. A dose relationship ($P < .05$) was seen in the incidence of endometrial hyperplasia and vaginal bleeding in the CEEs-only groups, with the highest incidence observed in the group taking CEEs at 0.625 mg/d. The incidence of breast pain in the CEEs-MPA groups also followed a dose relationship ($P < .05$), with

Figure 2. Spine Bone Mineral Density Changes for Modified Intention-to-Treat and Efficacy-Evaluable Populations for Conjugated Equine Estrogens (CEEs) Alone and CEEs-Medroxyprogesterone Acetate (MPA) Groups



Adjusted mean percentage changes (SE) in spine BMD over time are shown for the modified intention-to-treat (A and C) and efficacy-evaluable (B and D) populations for both the CEEs alone (A, B) and CEEs-MPA groups (C, D). The placebo group is displayed in all graphs. Changes were significantly different ($P < .05$) from baseline and placebo for all active treatment groups at all time points.

the highest incidence observed in the group taking CEEs at 0.625 mg/d and MPA at 2.5 mg/d. Throughout the 2-year study, adverse events led to the withdrawal of 8 of the 94 women (9%) in the placebo group and 103 of the 655 patients (16%) in the active treatment groups.

COMMENT

The Women's HOPE study is the first large, randomized placebo-controlled trial to evaluate BMD with lower doses of CEEs alone or combined with lower doses of MPA. Our data indicate that lower doses of CEEs (0.45 and 0.3 mg/d) with or without a lower dose of

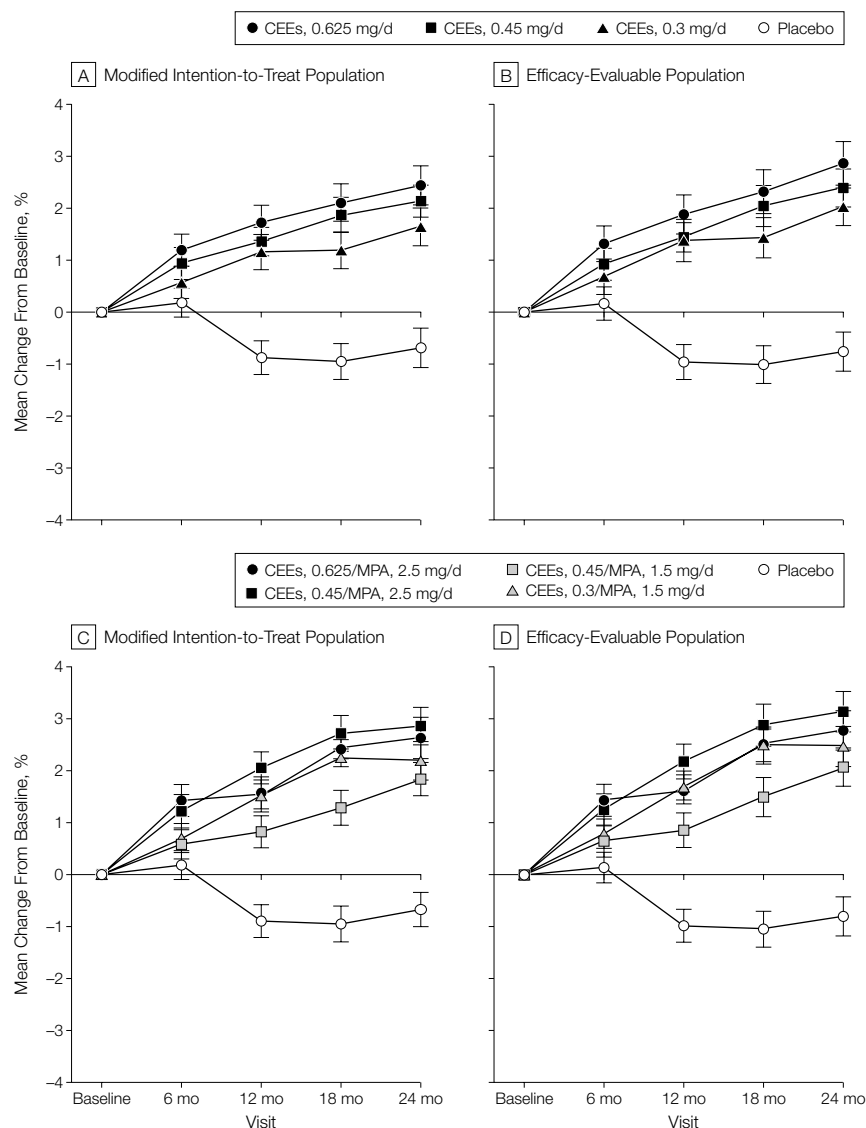
MPA (1.5 mg/d) prevented the loss of spine and hip BMD and reduced bone turnover in this population.

The significant increases in BMD observed in this study with CEEs only (0.3 mg/d) agree with those of Genant et al,⁴ who used calcium with esterified estrogens at 0.3 mg/d, and contradict earlier preliminary studies^{11,12} suggesting that doses of CEEs lower than 0.625 mg/d do not protect against postmenopausal bone loss. Our results showing the effectiveness of lower doses of CEEs combined with a lower dose of MPA are similar to those of small clinical trials of early postmenopausal women of different ethnic backgrounds, which have reported that CEEs at 0.3 mg/d combined with the commonly prescribed dose of MPA (2.5 mg/d) preserved bone density.^{7,16,20,21} Recker et al⁶ also reported similar improvements in older postmenopausal women treated with CEEs at 0.3 mg/d and MPA at 2.5 mg/d combined with 25-hydroxyvitamin D and calcium. Our results with lower-dose combination regimens do not support those of the CHART Study,⁵ which found no significant increase in BMD with ethinyl estradiol at 1 µg/d with norethindrone acetate at 0.2 mg/d and ethinyl estradiol at 2.5 µg/d with norethindrone acetate at 0.5 mg compared with baseline.

A dose-response effect for CEEs (0.625 mg/d was greater than 0.3 mg/d) was observed for changes in spine BMD but not the other BMD measures, which is not surprising, because the spine is more metabolically active than the hip. Genant et al¹² reported a 7-fold higher loss of vertebral cancellous bone than peripheral compact cortical bone in postmenopausal women after surgical menopause.

In the present study, the impact of MPA on CEEs was significant only for the increase in spine BMD and only for the 0.625-mg dose of CEEs. Similar findings were noted by Grey et al¹⁵ in their study of 23 women treated with a continuous combined regimen of CEEs at 0.625 mg/d with MPA at 5 mg/d for 1 year. In the large, randomized placebo-controlled, 3-year Postmeno-

Figure 3. Hip Bone Mineral Density Changes for Modified Intention-to-Treat and Efficacy-Evaluable Populations for Conjugated Equine Estrogens (CEE) Alone and CEEs-Medroxyprogesterone Acetate (MPA) Groups



Adjusted mean percentage changes (SE) in total hip BMD over time are shown for the modified intention-to-treat (A and C) and efficacy-evaluable (B and D) populations for both the CEEs alone (A, B) and CEEs-MPA groups (C, D). The placebo group is displayed in all graphs. Changes were significantly different ($P < .05$) from baseline for all active treatment groups at all time points. Changes were significantly different ($P < .05$) from placebo for all active treatment groups by 1 year.

pausal Estrogen/Progestin Interventions (PEPI) trial,¹⁴ the initial analysis showed a significantly higher increase in CEEs with continuous MPA in spinal BMD; however, no significant differences were found in BMD changes among the active treatments in adherent participants. At the lower CEE doses in the present study, neither dose of MPA resulted in gains in BMD or BMC that were significantly greater than those observed with CEEs alone. Gallagher and colleagues¹³ noted that MPA combined with CEEs (0.3 mg/d) for 2 years preserved spine BMD like CEEs only at 0.6 mg/d. However, in that study, 10 mg of MPA was used.

The time-course changes in BMD that we observed with CEEs only at 0.625 mg/d or combined continuously with MPA at 2.5 mg/d are also consistent with those reported for all participants in the PEPI trial.¹⁴ However, a direct comparison of the final change in BMD is impossible because our study was completed after 2 years, whereas the PEPI trial took 3 years to complete.

The relationship between BMD, fracture, and HRT has been reported in clinical trials using commonly prescribed doses.⁸⁻¹⁰ Although a fracture study in early postmenopausal women is impractical, further investigation is necessary to see whether the effects of lower doses of CEEs-MPA would result in a reduction of fractures in older postmenopausal women.

The importance of ERT and HRT for preserving bone mass is evidenced by the response of the placebo group. Women in this group lost significant amounts of BMD at all sites compared with baseline. The lack of change in bone turnover markers in the placebo group suggests that women in this study were likely to have received adequate calcium. Our findings support those of Dawson-Hughes et al,²² who noted that supplementation with calcium alone (500 mg/d) did not prevent the loss of BMD in early postmenopausal women. However, bone loss was less rapid in women who had been postmenopausal at least 6 years and whose usual dietary calcium intake was less than 400 mg/d.

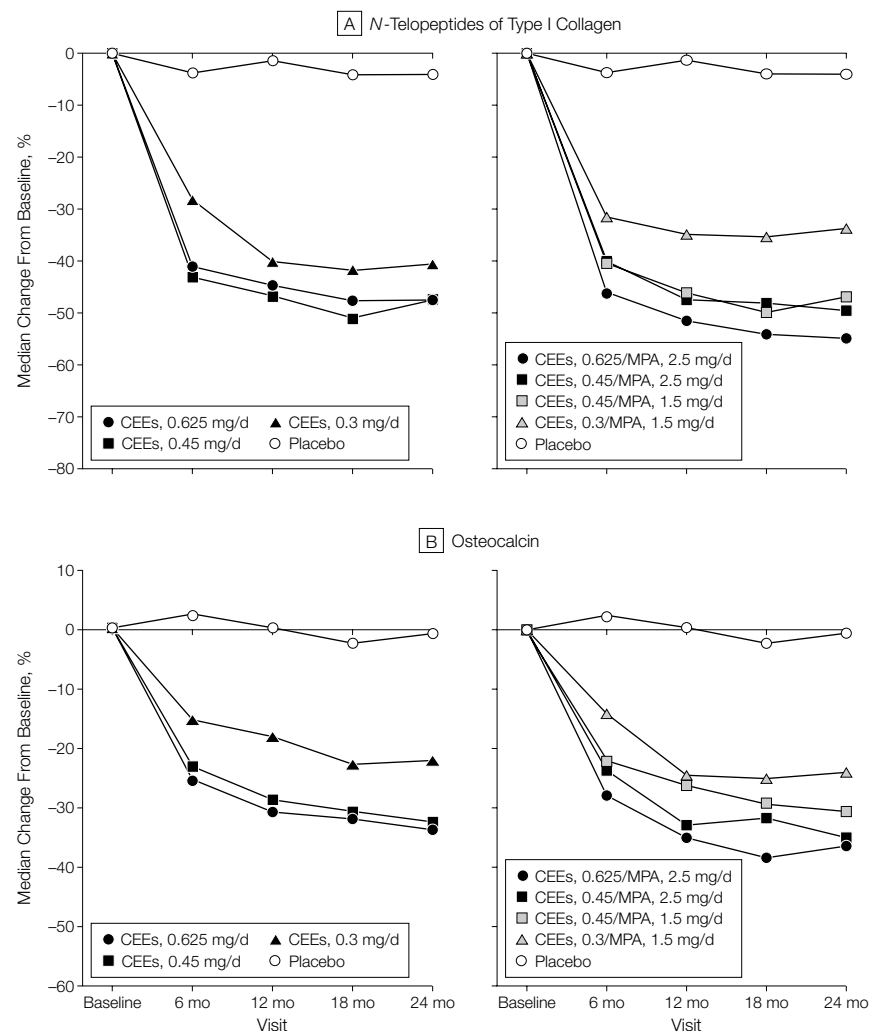
In summary, lower doses of CEEs or CEEs-MPA effectively reduce bone loss in early postmenopausal women. This substudy was part of the Women's HOPE study, a larger trial that demonstrated the beneficial effects of low-dose CEEs-MPA regimens on vasomotor symptoms and vaginal atrophy,¹⁸ lipid profiles,¹⁹ bleeding profiles,²³ and endometrial hyperplasia.²⁴ In addition, using lower doses of both estrogens and progestins makes clinical sense

and may enhance compliance with and initiation of therapy by enhancing the benefit-risk ratio.^{1,2}

Author Affiliations: Department of Internal Medicine, Helen Hayes Hospital, West Haverstraw, NY (Dr Lindsay); Bone Metabolism Unit, Creighton University School of Medicine, Omaha, Neb (Dr Gallagher); Division of Endocrinology, Wayne State University School of Medicine, Detroit, Mich (Dr Kleerekoper); and Clinical Research and Development, Wyeth Research, Philadelphia, Pa (Dr Pickar).

Author Contributions: Dr Kleerekoper, as an investigator in the Women's HOPE study, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Figure 4. Changes in Bone Markers for the Modified Intention-to-Treat (MITT) Population for Conjugated Equine Estrogens (CEEs) Only and CEEs-Medroxyprogesterone Acetate (MPA) Groups



Adjusted median percentage changes in urinary *N*-telopeptides of type I collagen (A) and serum osteocalcin (B) for the MITT population over time for the CEEs alone and placebo groups on the left and the CEEs-MPA and placebo groups on the right. Changes were significantly different ($P < .05$) from baseline and placebo for all active treatment groups at all time points.

sis. Dr Pickar had primary responsibility for obtaining funding and for administrative, technical, and material support, as well as supervision of the 19 substudy sites. **Study concept and design:** Lindsay, Gallagher, Kleerekoper, Pickar. **Acquisition of data:** Lindsay, Gallagher, Kleerekoper, Pickar. **Analysis and interpretation of data:** Lindsay, Gallagher, Kleerekoper, Pickar. **Drafting of the manuscript:** Lindsay, Gallagher, Kleerekoper, Pickar. **Critical revision of the manuscript for important intellectual content:** Lindsay, Gallagher, Kleerekoper, Pickar. **Obtained funding:** Gallagher, Pickar.

Statistical expertise: Lindsay, Gallagher, Kleerekoper, Pickar.

Administrative, technical, or material support: Lindsay, Kleerekoper, Pickar.

Study supervision: Lindsay, Kleerekoper, Pickar.

Funding/Support: Financial and material support for this research were provided by Wyeth Research. The Women's HOPE study investigators and Wyeth Research collaborated on the study design, analyses, and development of this article.

Role of Sponsor: The Women's HOPE study was funded and managed by Wyeth Research. The metabolic and osteoporosis substudy was conducted under the direction of the study investigators at the 19

substudy sites. Data monitoring was performed by regional clinical associates at Wyeth; quality control of BMD data was provided by the Bone Quality Control Center (Helen Hayes Hospital, West Haverhill, NY). Data analyses were performed by statisticians in clinical biostatistics at Wyeth.

Acknowledgment: We thank Thomas G. Cole, PhD, Director of the Core Laboratory for Clinical Studies, Washington University School of Medicine, St Louis, Mo, and his staff for analyses of blood and urine specimens. The statistical assistance of Yadong "Adam" Cui, PhD, and Bob Northington, PhD, and the editorial assistance of Karen Mittleman, PhD, are also appreciated.

REFERENCES

- Ettinger B. Personal perspective on low-dosage estrogen therapy for postmenopausal women. *Meno-pause*. 1999;6:273-276.
- Lobo RA, Whitehead MI. Is low-dose hormone replacement therapy for postmenopausal women efficacious and desirable? *Climacteric*. 2001;4:110-119.
- Connelly MT, Ferrari N, Hagen N, Inui TS. Patient-identified needs for hormone replacement therapy counseling: a qualitative study. *Ann Intern Med*. 1999;131:265-268.
- Genant HK, Lucas J, Weiss S, et al. Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. *Arch Intern Med*. 1997;157:2609-2615.
- Speroff L, Rowan J, Symons J, Genant H, Wilborn W, for the CHART Study Group. The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA*. 1996;276:1397-1403.
- Recker RR, Davies KM, Dowd RM, Heaney RP. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women: a randomized, controlled trial. *Ann Intern Med*. 1999;130:897-904.
- Gambacciani M, Ciaponi M, Cappagli B, Genazzani AR. Effects of low-dose continuous combined conjugated estrogens and medroxyprogesterone acetate on menopausal symptoms, body weight, bone density, and metabolism in postmenopausal women. *Am J Obstet Gynecol*. 2001;185:1180-1185.
- Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomized women. *Lancet*. 1980;2:1151-1154.
- Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women: a 5-year randomized trial. *Maturitas*. 1998;31:45-54.
- Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med*. 1992;117:1-9.
- Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol*. 1984;63:759-763.
- Genant HK, Cann CE, Ettinger B, Gordan GS. Quantitative computed tomography of vertebral spongiosa: a sensitive method for detecting early bone loss after oophorectomy. *Ann Intern Med*. 1982;97:699-705.
- Gallagher JC, Kable WT, Goldgar D. Effect of progestin therapy on cortical and trabecular bone: comparison with estrogen. *Am J Med*. 1991;90:171-178.
- Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1996;276:1389-1396.
- Grey A, Cundy T, Evans M, Reid I. Medroxyprogesterone acetate enhances the spinal bone mineral density response to oestrogen in late postmenopausal women. *Clin Endocrinol*. 1996;44:293-296.
- Mizunuma H, Okano H, Soda M, et al. Prevention of postmenopausal bone loss with minimal uterine bleeding using low dose continuous estrogen/progestin therapy: a 2-year prospective study. *Maturitas*. 1997;27:69-76.
- Riggs BL, Melton LJ III. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone*. 1995;17:505S-511S.
- Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril*. 2001;75:1065-1079.
- Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. *Fertil Steril*. 2001;76:13-24.
- Webber CE, Blake JM, Chambers LF, Roberts JG. Effects of 2 years of hormone replacement upon bone mass, serum lipids and lipoproteins. *Maturitas*. 1994;19:13-23.
- MacLennan AH, MacLennan A, Wenzel S, Chambers HM, Eckert K. Continuous low-dose oestrogen and progestogen hormone replacement therapy: a randomized trial. *Med J Aust*. 1993;159:102-106.
- Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med*. 1990;323:878-883.
- Archer DF, Dorin M, Lewis V, Schneider DL, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on endometrial bleeding. *Fertil Steril*. 2001;75:1080-1087.
- Pickar JH, Yeh I-T, Wheeler JE, Cunnane MF, Speroff L. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril*. 2001;76:25-31.