Title

The effect of hormone therapy on mean blood pressure and visit-to-visit blood pressure variability in postmenopausal women

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THE EFFECT OF HORMONE THERAPY ON MEAN BLOOD PRESSURE AND VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY IN POSTMENOPAUSAL WOMEN: RESULTS FROM THE WOMEN'S HEALTH INITIATIVE RANDOMIZED CONTROLLED TRIALS

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Abstract

Objectives—Mean and visit-to-visit variability (VVV) of blood pressure are associated with an increased cardiovascular disease risk. We examined the effect of hormone therapy on mean and VVV of blood pressure in postmenopausal women from the Women's Health Initiative (WHI) randomized controlled trials.

Methods—Blood pressure was measured at baseline and annually in the two WHI hormone therapy trials in which 10,739 and 16,608 postmenopausal women were randomized to conjugated equine estrogens (CEE, 0.625 mg/day) or placebo, and CEE plus medroxyprogesterone acetate (MPA, 2.5 mg/day) or placebo, respectively.

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Conflicts of Interest: There are no other potential conflicts of interest.

List of Supplemental Digital Content

Supplemental Digital Content 1 (which contains Supplementary Methods, Supplementary Tables 1–5, WHI Administrative Information, and Supplementary Figures 1–2).

Results—At the first annual visit (Year 1), mean systolic blood pressure was 1.04 mmHg (95% CI 0.58, 1.50) and 1.35 mmHg (95% CI 0.99, 1.72) higher in the CEE and CEE+MPA arms respectively compared to corresponding placebos. These effects remained stable after Year 1. CEE also increased VVV of systolic blood pressure (ratio of VVV in CEE vs. placebo, 1.03, P<0.001), whereas CEE+MPA did not (ratio of VVV in CEE+MPA vs. placebo, 1.01, P=0.20). After accounting for study drug adherence, the effects of CEE and CEE+MPA on mean systolic blood pressure increased at Year 1, and the differences in the CEE and CEE+MPA arms vs. placebos also continued to increase after Year 1. Further, both CEE and CEE+MPA significantly increased VVV of systolic blood pressure (ratio of VVV in CEE vs. placebo, 1.04, P<0.001; ratio of VVV in CEE+MPA vs. placebo, 1.05, P<0.001).

Conclusions—Among postmenopausal women, CEE and CEE+MPA at conventional doses increased mean and VVV of systolic blood pressure.

Keywords

hypertension; blood pressure; postmenopause; women; hormone therapy

Introduction

Evidence from randomized controlled trials has suggested that menopausal hormone therapy has unfavorable effects on clinical outcomes including cardiovascular disease (CVD) and stroke [1, 2]. Presently, hormone therapy is primarily recommended for the treatment of perimenopausal symptoms, particularly in women younger than 60 years of age [3].

Hypertension is a major risk factor for stroke, myocardial infarction, heart failure, and atrial fibrillation [4]. Some evidence suggests that hormone therapy may have beneficial effects on some of the mechanisms hypothesized to be involved in the development of hypertension including abnormal baroreceptor sensitivity, increased sympathetic tone, and arterial stiffness [5–7]. However, previous studies examining the association between hormone therapy and blood pressure have produced divergent results with some studies reporting an increase in blood pressure levels or a higher risk of hypertension while other studies reporting a neutral or antihypertensive effect of hormone therapy [8–12]. These prior studies were typically limited by small sample sizes, cross-sectional design, and a lack of a comparison group not taking hormone therapy. Further, few double-blinded, placebo controlled randomized controlled trials have examined the effect of hormone therapy on blood pressure in postmenopausal women.

Increased visit-to-visit variability (VVV) of blood pressure is associated with a higher risk of cardiovascular events, independent of mean blood pressure and other possible explanatory factors [13, 14]. We previously reported that higher VVV of systolic blood pressure was independently associated with an increased risk of stroke in postmenopausal women from the Women's Health Initiative (WHI) trials [14]. Thus far, only a few studies have examined the effect of hormone therapy on blood pressure variability over a 24-hour period [15, 16] and no study, to our knowledge, has examined the effect of hormone therapy on VVV of blood pressure. Therefore, in the present study, we determined the effect of conjugated equine estrogen (CEE) alone and CEE plus medroxyprogesterone acetate (MPA)

on mean blood pressure and VVV of blood pressure in postmenopausal women from the WHI hormone therapy randomized controlled trials.

Methods

Sample Population

The WHI hormone therapy trials enrolled 27,347 US postmenopausal women 50 to 79 years of age from 1993 to 1998 [1, 2]. Women were excluded for a variety of reasons including competing medical conditions, concerns about safety, adherence or retention risks, as well as anticoagulant use [17]. In the CEE trial, postmenopausal women with a history of a hysterectomy (n=10,739) were randomized to receive 0.625 mg oral CEE (Premarin) or matching placebo daily [2]. In the CEE+MPA trial, postmenopausal women with an intact uterus (n=16,608) were randomized to receive 0.625 mg oral CEE + 2.5mg oral MPA (Prempro) or matching placebo daily [1]. Study drug for both trials was administered in a double-blind manner. The planned end date of treatment was 2005 for a mean follow-up of 8.5 years; however, CEE+MPA trial medications were stopped in 2002 and CEE medications were stopped in 2004 after mean follow-up periods of 5.6 and 7.1 years, respectively [1, 2]. These follow-up periods were used for the present analyses. The protocols were approved by institutional review boards of the participating institutions; all trial participants provided written informed consent.

Blood Pressure and Heart Rate Measurement

In the CEE and CEE+MPA trials, blood pressure and heart rate were measured at baseline and each post baseline annual follow-up visit by certified staff using standardized procedures and instruments. Appropriate cuff bladder size was determined at each visit based on arm circumference. Blood pressure was measured in the right arm with a mercury sphygmomanometer after the participant was seated and had rested for 5 minutes; 2 measures, taken 30 seconds apart, were recorded. Heart rate was measured manually once at each visit.

Definitions of a Participant's Blood Pressure at each Visit, and Randomization Group Mean and VVV of Blood Pressure

A participant's blood pressure at each visit was calculated as the mean of the 2 measurements. Mean and VVV of blood pressure were determined by randomization group. For each participant, blood pressure trajectories across visits were estimated using linear mixed effects (LME). Mean blood pressure by randomization group was estimated by averaging the participant-specific blood pressure trajectories over the annual visits for each group. Group-specific VVV was defined as the variation of participants' observed blood pressure around their respective trajectories, for each randomization group. The group-specific definition of VVV complements participant-specific definitions of VVV (SD and SDreg), as described previously [13, 14, 18]. The Supplemental Digital Content (Supplementary Methods) provides additional details regarding the estimation of mean and VVV of blood pressure for the present study.

Statistical Analyses

The Supplemental Digital Content (Supplementary Methods) provides additional details regarding the ascertainment and definition of participant baseline characteristics and covariates. Baseline characteristics of participants were compared by randomization arm in both trials. For the primary analyses, we modeled systolic blood pressure at baseline and during follow-up using longitudinal data analyses that were based on the intention-to-treat principle. A piecewise LME model was used to assess the effect of hormone therapy on systolic blood pressure at the first annual visit (i.e., difference in means at Year 1; active treatment minus placebo) and whether the effect of hormone therapy changed through the remainder of follow-up (i.e., difference in annual change after Year 1; active treatment minus placebo). The effect of hormone therapy on VVV of systolic blood pressure was assessed by dividing group estimates of within-participant variability (the ratio of VVV in the active treatment vs. placebo arms) and statistical significance based on a test of heterogeneity for the VVV between groups. These models were adjusted for age, race/ethnicity, body mass index, and use of anti-hypertensive medications at baseline. The Supplemental Digital Content (Supplementary Methods) provides further information on how the effects of hormone therapy on mean and VVV of systolic blood pressure were estimated.

Several exploratory subgroup analyses according to selected baseline characteristics were performed. The subgroup analysis of mean systolic blood pressure included the subgroup variable and the hormone therapy × subgroup interaction variables, and the statistical significance of interaction was tested. In contrast to mean blood pressure, interactions for the effect of hormone therapy on VVV cannot be directly examined in a LME model. Instead, the effect of hormone therapy on VVV of systolic blood pressure was examined in analyses stratified by subgroup (i.e. examining the effect of hormone therapy on VVV within a particular subgroup): a k-degree of freedom test for heterogeneity was used to determine whether the VVV between randomization groups differed for any of the k-levels of a particular subgroup. Fifteen baseline characteristics were examined for each hormone therapy trial for both mean systolic blood pressure and VVV, so six statistically significant tests ($p<0.05$) would be expected on the basis of chance alone.

Analyses for systolic blood pressure were stratified by antihypertensive medication use at baseline. As previous studies have suggested that calcium channel blockers and diuretics are associated with reductions in mean blood pressure and VVV [19], antihypertensive medications at baseline were further classified into use of calcium channel blockers without diuretics, use of diuretics without calcium channel blockers, and use of other medications. A sensitivity analysis was conducted to control for adherence, in which non-adherent women were censored and inverse probability weighting was used to assure that randomization arms remained balanced and that statistical estimates were valid. As described in the Supplementary Methods (see Supplemental Digital Content), adherence to study medications (either hormone therapy or corresponding placebo) was monitored at a clinic visit six months and twelve months after randomization and annually thereafter. Adherence to medications was monitored by weighing returned bottles if available, or by self-report for the small percentage of women with a missed pill collection. A participant was classified as

non-adherent if she took <80% of study pills (estimated by weight), stopped taking study pills (by self-report if a pill collection was missed), or began taking non-WHI hormone therapy. An additional sensitivity analysis also added a sensible constant (10 mmHg) [20] to systolic blood pressure after a participant reported incident hypertension. Finally, participant-specific VVV (SD and SDreg) of systolic blood pressure [14] were computed for each participant and then randomization groups were compared (see Supplementary Methods, Supplemental Digital Content).

The primary analyses were repeated for diastolic blood pressure (for the main effects and subgroup analyses), and then separately for pulse pressure (for main effects analysis only). Analyses of mean and VVV of blood pressure were pre-specified in our study but not pre-specified in the original WHI hormone therapy trials. All statistical tests were two sided and P values <0.05 were considered to be statistically significant. Analyses were performed using SAS statistical software version 9.2 (SAS Inc, Cary, NC) and figures were constructed by using R version 2.11 [21].

Results

Participant Characteristics of the CEE and CEE+MPA Trials

Supplementary Table 1 (Supplemental Digital Content) shows the baseline characteristics of the participants by randomization arm in the CEE and CEE+MPA trials. In the CEE trial, there was a significantly higher prevalence of bilateral oophorectomy in the placebo arm vs. the CEE arm. There were no other significant differences in baseline characteristics between the active medication and placebo arms in the CEE and CEE+MPA trials.

Effect of CEE on Mean Systolic Blood Pressure

In the CEE trial (Table 1 and 1st panel of Supplementary Figure 1), mean systolic blood pressure during the intervention period was significantly higher in the CEE arm vs. the placebo arm (P-Fit<0.001). Mean systolic blood pressure was 1.04 (95% CI 0.58, 1.50; P<0.001) mmHg higher in the CEE arm than in the placebo arm at Year 1. After Year 1, the difference in mean systolic blood pressure between treatment arms did not further increase and remained stable (difference in annual change 0.07, 95% CI −0.05, 0.19 mmHg/year, P=0.25).

There was no interaction between CEE and baseline antihypertensive medication use on mean systolic blood pressure (Table 1 and 2nd panel of Supplementary Figure 1). There also was no interaction (P=0.26) between CEE and baseline antihypertensive medication category (calcium channel blockers without diuretics, diuretics without calcium channel blockers, and other medications). The results for the primary analysis and interaction analysis for baseline antihypertensive medication use did not change after excluding Year 1 blood pressure measurements (data not shown). As shown in Table 1, the effect of CEE on mean systolic blood pressure at follow-up visits was modified by age (interaction P-Fit=0.01), race/ethnicity (interaction P-Fit<0.001), and a history of CVD (interaction P-Fit=0.003). The effect of CEE on mean systolic blood pressure at follow-up visits was similar across other prespecified subgroups. The difference in mean systolic blood pressure

at Year 1 between the CEE vs. placebo was significantly greater in younger participants particularly among women aged 50–54 years (P=0.004). Additional analyses indicated that this CEE × age interaction was not modified by bilateral oophorectomy status (3-way interaction P-Fit=0.95). At Year 1, the systolic blood pressure difference associated with CEE vs. placebo was also significantly greater in White and Hispanic participants (P=0.003) and in participants without CVD history (P<0.001). The difference in annual change of systolic blood pressure after Year 1 between the CEE arm and placebo arm was similar across these subgroups (P>0.05 for all).

After accounting for study drug adherence by censoring non-adherent participants, the difference in mean systolic blood pressure at Year 1 increased to 1.13 (95% CI 0.52, 1.74) mmHg (P<0.001). Further, the difference in annual change of systolic blood pressure after Year 1 increased and was statistically significant (0.25, 95% CI 0.07, 0.43 mmHg/year, P=0.008), indicating that the effect of CEE on mean systolic blood pressure continued to increase after Year 1. Supplementary Figure 1 (3rd panel) shows the effect of CEE on mean systolic blood pressure at follow-up visits stratified by baseline antihypertensive medication use and after accounting for study drug adherence. Further, as the Supplementary Figure 1 (4th panel) shows, additionally accounting for antihypertensive medication use during follow-up in participants not taking antihypertensive medications at baseline further increased the effect of CEE at Year 1 and also throughout the remainder of follow-up after Year 1.

Effect of CEE+MPA on Mean Systolic Blood Pressure

In the entire sample (Table 2 and 1st panel of Supplementary Figure 2), mean systolic blood pressure was significantly higher in the CEE+MPA arm vs. the placebo arm (P-Fit<0.001). The systolic blood pressure was 1.35 (95% CI 0.99, 1.72) mmHg higher in the CEE+MPA arm (P<0.001) than the placebo arm at Year 1 (Table 2). The difference in mean systolic blood pressure between treatment arms did not further increase and remained stable after Year 1 (difference in annual change 0.09, 95% CI −0.03, 0.21 mmHg/year, P=0.14). There was no interaction between CEE+MPA and baseline antihypertensive medication use on mean systolic blood pressure at follow-up visits (Table 2 and 2nd panel of Supplementary Figure 2). There was also no interaction (P=0.20) between CEE+MPA and baseline antihypertensive medication category. The results did not change after excluding Year 1 blood pressure measurements (data not shown). As shown in Table 2, the effect of CEE +MPA on mean systolic blood pressure was modified by baseline systolic blood pressure (interaction P-Fit<0.001), smoking status (interaction P-Fit=0.03), and vasomotor symptoms (interaction P-Fit=0.04). The effect of CEE+MPA at Year 1 was significantly greater in participants with higher baseline systolic blood pressure (P<0.001), whereas the effect after Year 1 was similar across baseline systolic blood pressure levels. The difference associated with CEE+MPA between the intervention arms was greatest among nonsmokers and participants that were not experiencing moderate or severe vasomotor symptoms for whom the stronger effects were additive and could not be solely attributed to either differences at Year 1 or the subsequent follow-up period. The association between CEE+MPA and mean systolic blood pressure at follow-up visits was similar across other prespecified subgroups.

After accounting for study drug adherence, the difference in mean systolic blood pressure at Year 1 increased to 1.48 (95% CI 1.02, 1.93) mmHg (P<0.001). Further, the effect of CEE +MPA after Year 1 (i.e. the difference in annual change of systolic blood pressure) increased to 0.28 (95% CI 0.11, 0.45) mmHg/year and was statistically significant (P=0.001). Supplementary Figure 2 (3rd panel) shows the effect of CEE+MPA on mean systolic blood pressure at follow-up visits stratified by baseline antihypertensive medication use and after accounting for study drug adherence. Supplementary Figure 2 (4th panel) shows the sensitivity analysis, which accounts for antihypertensive medication use during follow-up in participants not taking antihypertensive medications at baseline.

Effects of CEE and CEE+MPA on VVV of Systolic Blood Pressure

In the CEE trial (Table 1), there was a small but statistically significant difference in VVV of systolic blood pressure across visits between the CEE and placebo arms (ratio of VVV of systolic blood pressure in CEE vs. placebo arms, 1.03, P<0.001). In contrast, in the CEE +MPA trial (Table 2), there was no significant difference in VVV of systolic blood pressure across visits between the CEE+MPA and placebo arms (ratio of VVV of systolic blood pressure in CEE+MPA vs. placebo arms, 1.01, P=0.20). The results for both trials did not change in analyses that excluded the baseline visit (data not shown). Ratios of VVV of systolic blood pressure stratified by various subgroups in the CEE and CEE+MPA trials are provided in Tables 1 and 2 respectively. In the CEE trial, similar to the entire sample, the effect of CEE on VVV of systolic blood pressure was statistically significant across all subgroups including baseline antihypertensive medication use (P<0.001 for all). This difference was also statistically significant (P<0.001) across baseline antihypertensive medication categories. In the CEE+MPA trial, similar to the entire sample, the stratified analysis showed that there was no significant difference in VVV of systolic blood pressure between the CEE+MPA versus placebo arm in subgroups of baseline antihypertensive medication use (P=0.31), or antihypertensive medication categories (P=0.52). However, CEE+MPA was significantly associated with an increase in VVV of systolic blood pressure in women who were 5 to <10 years and ≥15 years from menopause (P=0.01), who had no or mild vasomotor symptoms (P=0.02), had higher mean systolic blood pressure at baseline (P<0.001), never smoked (P=0.04), and had left ventricular hypertrophy (P=0.01). The effect of CEE+MPA was not significant in the remaining subgroups.

In sensitivity analyses, participant-specific VVV (SD and SDreg) were computed for each participant and then randomization groups were compared. The results for participant-specific VVV were similar to the results for group-specific VVV. The ratio of SD between the hormone therapy arm and placebo arm was 1.03 (P=0.002) for the CEE trial and 1.01 (P=0.11) for the CEE+MPA trial. These ratios correspond to absolute differences in SD of 0.3 mmHg and 0.2 mm Hg respectively. Likewise, the ratio of SDreg between the hormone therapy arm and placebo arm was 1.03 (P=0.003) for the CEE trial, and 1.00 (P=0.62) for the CEE+MPA trial. These ratios correspond to absolute differences in SD of 0.2 mmHg and 0.1 mm Hg respectively.

After accounting for study drug adherence, the difference in VVV of systolic blood pressure between CEE and placebo arms increased (ratio of VVV of systolic blood pressure in CEE

vs. placebo arms, 1.04, P<0.001). Further, the difference in VVV of systolic blood pressure between the CEE+MPA and placebo arms increased and was now statistically significant (ratio of VVV of systolic blood pressure in CEE+MPA vs. placebo arms, 1.05, P<0.001).

Effects of CEE and CEE+MPA on Mean and VVV of Diastolic Blood Pressure

Mean diastolic blood pressure during the intervention period (Supplementary Table 2) was not different between the CEE arm vs. the placebo arm (P-Fit=0.59). As was found with systolic blood pressure, the effect of CEE on mean diastolic blood pressure was modified by age (interaction P-Fit=0.003) and race/ethnicity (interaction P-Fit=0.01). Similarly, the CEE × age interaction was not modified by bilateral oophorectomy status (3-way interaction P-Fit=0.92). The effect of CEE on mean diastolic blood pressure was also modified by years since menopause (interaction P-Fit=0.03) and prior hormone use (interaction P-Fit=0.02). There was no significant difference in VVV of diastolic blood pressure between the CEE and placebo arms (ratio of VVV of diastolic blood pressure in CEE vs. placebo arms, 1.00, P=0.51). CEE significantly increased VVV of diastolic blood pressure in Black women (Supplementary Table 2).

Mean diastolic blood pressure during the intervention period was not different between the CEE+MPA arm vs. the placebo arm (Supplementary Table 3, P-Fit=0.26). The effect of CEE+MPA on mean diastolic blood pressure was modified by age (interaction P-Fit=0.02) and race/ethnicity (interaction P-Fit=0.02). VVV of diastolic blood pressure was modestly *lower* in the CEE+MPA arm vs placebo arm (ratio of VVV of diastolic blood pressure in CEE+MPA vs. placebo arms, 0.99, P=0.03). Further analysis showed that CEE+MPA significantly decreased VVV of diastolic blood pressure in the following subgroups: women who were <15 years from menopause, past or current users of hormone therapy, had body mass index <30 kg/m^2, never smoked or smoked in the past, and those without left ventricular hypertrophy.

Effects of CEE and CEE+MPA on Mean and VVV of Pulse Pressure

Supplementary Tables 4 and 5 show the effects of CEE and CEE+MPA respectively on mean and VVV of pulse pressure. The results are similar to the effects of CEE and CEE +MPA on mean and VVV of systolic blood pressure at Year 1 and after Year 1.

Discussion

In the WHI hormone therapy trials, treatment with either CEE or CEE+MPA increased mean systolic blood pressure compared with placebo. This effect was observed at Year 1 and remained stable throughout the rest of the follow-up period. Treatment with CEE significantly increased VVV of systolic blood pressure whereas treatment with CEE+MPA did not. After accounting for study drug adherence, the effects of CEE and CEE+MPA on mean systolic blood pressure were stronger at Year 1 and the differences between the intervention arms continued to increase after Year 1; in addition, both CEE and CEE+MPA increased VVV of systolic blood pressure. Finally, CEE and CEE+MPA had no significant effects on mean diastolic blood pressure and no consistent effects on VVV of diastolic blood pressure.

Several observational studies have previously examined the effect of hormone therapy on blood pressure [8–12]. Some studies reported an increase in blood pressure levels or a higher risk of hypertension [8, 11] while other studies reported either a neutral [9] or an antihypertensive effect of hormone therapy [10]. Differences in study design, size and characteristics of the study populations, the type of hormone therapy received (i.e. unopposed estrogen or estrogen plus progesterone), and the dose and type of formulation of hormone therapy (oral or transdermal) may all explain the discrepant results of these studies.

Few randomized controlled trials have examined the effect of hormone therapy on blood pressure, and far fewer have been placebo controlled [22, 23]. For example, Scott et al. [22] showed in a randomized placebo controlled trial of diabetic postmenopausal women (n=150) that 2 mg oral estradiol hemihydrate and 1 mg oral norethisterone acetate (Kliofem) daily had no effect on systolic nor diastolic blood pressure over 1 year follow-up. Steiner et al. [23] examined the effect of 17B-estradiol on blood pressure in the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) in which a total of 222 healthy postmenopausal women were randomly assigned to either 1 mg oral micronized 17B-estradiol daily or placebo daily for 2 years. Compared with the placebo group, estrogen use did not change systolic or diastolic blood pressure. However, treatment effects on systolic blood pressure differed significantly by participant age with younger postmenopausal women on estradiol having a greater increase in systolic blood pressure.

Our study adds important information to the existing literature on the effects of hormone therapy on blood pressure. In two large randomized trial components of WHI, we demonstrated that in postmenopausal women, oral CEE and CEE+MPA at conventional doses both increased mean systolic blood pressure. In addition to White and Hispanic participants and in participants without CVD history, the effect of CEE on mean systolic blood pressure was stronger in younger postmenopausal women, particularly in the 50–54 years age range. This latter finding is consistent with the findings from prior studies that showed that younger women have greater increases in blood pressure with hormone therapy use [8, 23]. The effect of CEE+MPA was stronger in participants with higher baseline systolic blood pressure, among nonsmokers and participants that were not experiencing moderate or severe vasomotor symptoms. In contrast to the CEE trial, there was no interaction of age on the effect of CEE+MPA on systolic blood pressure. The reasons for these dissimilar findings are unclear.

Comparison of the CEE and CEE+MPA groups to corresponding placebo groups was a major strength our study brings to the published literature. In the CEE arm (see 1st panel of Supplementary Figure 1), mean systolic blood pressure continuously decreased over the follow-up period. In the CEE+MPA arm (see 1st panel of Supplementary Figure 2), mean systolic blood pressure decreased and then increased over the follow-up period with a neutral net effect. In the absence of the placebo groups, these findings would lead one to incorrectly conclude that CEE has beneficial effects on systolic blood pressure whereas CEE +MPA has neutral effects. Similar to prior placebo controlled trials of antihypertensive medications [24], in our study, systolic blood pressure in the placebo arm over the follow-up period was lower than at baseline. However, it was consistently lower than in the CEE alone or CEE+MPA arms during the intervention period. Stratification of each hormone therapy

trial by baseline antihypertensive medication use was also informative. In those women on antihypertensive medications at baseline, CEE or CEE+MPA attenuated the decrease in mean systolic blood pressure over the follow-up period (see 2nd panel of Supplementary Figures 1 and 2). In contrast, in women not on antihypertensive medications at baseline, CEE or CEE+MPA increased mean systolic blood pressure to a level that was greater than at baseline. These effects were stronger when accounting for antihypertensive medication use during follow-up.

In the CEE trial, hormone therapy consisted of 0.625 mg/day of oral CEE (Premarin), and in the CEE+MPA trial, hormone therapy consisted of 0.625 mg/day of oral CEE plus 2.5 mg/day of oral medroxyprogesterone acetate (Prempro). In the recent Kronos Early Estrogen Prevention Study (KEEPS) [25], healthy women (n=727) who entered menopause within the past three years were randomized to either low dose oral CEE (0.45 mg/day) or transdermal estrogen (0.05 mg/day), both with cyclic oral micronized progesterone (200 mg/day for 12 days/month); or matching placebo for 4 years. Neither low dose oral CEE or transdermal estrogen with cyclic oral progesterone was associated with changes in systolic or diastolic blood pressure. Therefore, the effects of hormone therapy on blood pressure may vary as a function of dose and/or mode of delivery.

Increased VVV of systolic blood pressure is associated with a higher risk of CVD events [13, 14] and all-cause mortality [18]. Little is known about what factors increase VVV of blood pressure. Animal studies suggest that hormone therapy may affect beat-to-beat blood pressure variability [26]. Further, human studies suggest that hormone therapy may also affect ambulatory blood pressure variability over a 24-hour period in postmenopausal women [15]. Szekacs et al. [15] showed in an uncontrolled study that a combination of estradiol and norgestrel for 19 weeks reduced ambulatory blood pressure variability in 34 postmenopausal women with treated hypertension. However, no effect of 17B-oestradiol and norethisterone acetate on ambulatory blood pressure variability was observed in a similar study by Kawecka-Jaszcz et al. [16]. In our study, only CEE significantly increased VVV of systolic blood pressure; treatment with CEE and CEE+MPA both increased VVV of systolic blood pressure in analyses that took into consideration study drug adherence.

The effects of CEE alone and CEE+MPA on mean systolic blood pressure were relatively small in our study at Year 1 (1.04, 95% CI 0.58–1.50, mmHg, higher in the CEE trial, and 1.35, 95% CI 0.99–1.72, mmHg higher in the CEE+MPA trial). After accounting for study drug adherence, the effects of hormone therapy on mean systolic blood pressure were stronger at Year 1 and the differences between intervention arms continued to increase annually after Year 1. Although modest, these effects on systolic blood pressure may have a greater impact on a population level. Using results from a previous meta-analysis of 61 prospective studies [27], it is estimated for women aged 50–79 years old, stroke mortality and ischemic heart disease mortality both increase by approximately 5 to 6% for every 1.5 mm Hg increase in systolic blood pressure. Therefore, the effects on systolic blood pressure as observed in our study may be clinically relevant for a large population of postmenopausal women who begin and are maintained on hormone therapy for perimenopausal symptoms. These findings may be particularly relevant as the numbers of postmenopausal women are expected to increase substantially with the projected growth of the older US population in

the coming decades. Our study also identified several subgroups of postmenopausal women who were at disproportionally higher risk for larger hormone therapy-induced increases in systolic blood pressure. For example, in Hispanic women, CEE increased systolic blood pressure at Year 1 by 4.06 mmHg. Women who demonstrated greater hormone therapy-induced increases in systolic blood pressure may be at greater risk for CVD events. Finally, the absolute differences in VVV between the hormone therapy arm and the placebo arm in the CEE trial and CEE+MPA trial were small. It is unclear whether such modest differences in VVV are clinically meaningful with respect to VVV-related outcomes in postmenopausal women [14]. Future studies are needed to expand on the results of the present study, and to determine the extent to which observed adverse effects of hormone therapy on mean and VVV of systolic blood pressure explain increases in the risk of CVD including stroke that are attributed to hormone therapy use.

Finally, in our study, CEE and CEE+MPA both increased mean pulse pressure, an indirect measure of arterial stiffness. Given that arterial stiffness is associated with incident hypertension [28] and also higher VVV of systolic blood pressure [29, 30], it is possible that hormone therapy-induced increases in mean and VVV of systolic blood pressure in the WHI hormone therapy trials are partially explained by the adverse effects of hormone therapy on arterial stiffness. However, several small observational and randomized studies of postmenopausal women in addition to animal studies have produced disparate results of the effects of hormone therapy on more direct measures of arterial stiffness including pulse wave velocity, distensibility and compliance [31–33]. Future research should clarify the role of arterial stiffness in the effects of hormone therapy on mean and VVV of systolic blood pressure.

Major strengths of the study are the well-characterized study population and the randomized placebo controlled design of the WHI hormone therapy trials. Further, the very large sample sizes for each of the trial components allowed for the examination of the effects of hormone therapy on blood pressure across various subgroups. An additional strength of the study was the careful and standardized assessment of blood pressure. Further, the participants in WHI represent a diverse ethnic, geographic, and socioeconomic sample of women in the United States, which increases the generalizability of the study results.

Some limitations should be acknowledged. It is possible that blood pressure readings were affected by measurement error in our study. However, since the presence of measurement error would have biased our results toward the null, it is likely that the effect of hormone therapy on mean systolic blood pressure and VVV of systolic blood pressure would be even stronger if measurement error were eliminated. Further, the primary analyses focused on the main effects of CEE and CEE+MPA on mean and VVV of systolic blood pressure. The results of the subgroup analyses and for diastolic blood pressure should be considered exploratory, and false positives are possible, given the number of comparisons that were conducted for these latter analyses. At each visit, blood pressure was measured in one arm. Some guidelines [34] have recommended that blood pressure be measured in both arms with the highest value used as the reference arm in the presence of an interarm difference. However, the randomized controlled design element of both hormone therapy trials eliminates any issues related to the arm in which blood pressure is measured. Further, the

approach in WHI for blood pressure measurement is consistent with several population-based studies [35, 36] or other large randomized controlled trials [37]. Finally, hormone therapy is no longer accepted as an effective preventive strategy for chronic disease onset in older women [3]. Although hormone therapy is still being prescribed for women with vasomotor symptoms, the overall implications of our findings in clinical practice may be limited.

In conclusion, the results from two large placebo controlled randomized trials of postmenopausal women suggest that treatment with either oral CEE or CEE+MPA at conventional doses modestly increased mean systolic blood pressure over the follow-up period. There was no interaction of baseline antihypertensive medication use and the effects of CEE or CEE+MPA on mean systolic blood pressure. Further, treatment with CEE significantly increased VVV of systolic blood pressure whereas treatment with CEE+MPA did not. After accounting for study drug adherence, the effects of CEE and CEE+MPA on mean and VVV of systolic blood pressure increased in magnitude and were statistically significant. These findings suggest that long-term use of hormone therapy may have adverse effects on mean and VVV of systolic blood pressure. Future studies should examine the degree to which these effects mediate the link between oral CEE or CEE+MPA at conventional doses and a higher risk of CVD including stroke in postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Effects* of CEE on Mean Systolic Blood Pressure (SBP) and Visit-to-Visit Variability (VVV†) of SBP During the Women's Health Initiative CEE Randomized Controlled Trial (n=10,739)

			SBP			VVV of SBP
Subgroup	**Active (N)**	**Placebo (N)**	**Difference‡ of SBP (95%CI) at Y1**	**Difference§ of slopes (95%CI) after Y1**	**P-Fit‖**	**Ratio of VVV¶**
Overall	**5,310**	**5,429**	**1.04 (0.58, 1.50)**	**0.07 (−0.05, 0.19)**	**<0.001**	**1.03**
Age, yrs					0.01	
50–54	687	709	2.29 (1.15, 3.43)	−0.10 (−0.38, 0.18)		1.06
55–59	952	965	1.12 (0.10, 2.15)	0.05 (−0.20, 0.31)		1.03
60–69	2386	2465	1.28 (0.59, 1.96)	0.04 (−0.14, 0.21)		1.03
70–79	1285	1290	−0.28 (−1.31, 0.74)	0.25 (−0.02, 0.52)		1.02
Race/Ethnicity					<0.001	
White	4009	4075	1.07 (0.54, 1.59)	0.14 (0.00, 0.27)		1.02
Black	781	835	−0.17 (−1.44, 1.09)	−0.14 (−0.46, 0.19)		1.04
Hispanic	319	332	4.06 (2.21, 5.91)	−0.28 (−0.75, 0.20)		1.10
Asian	86	78	−0.09 (−3.96, 3.78)	0.08 (−0.92, 1.09)		1.05
Years since menopause					0.33	
<5	331	325	1.50 (−0.18, 3.19)	0.03 (−0.40, 0.45)		1.08
5–<10	496	492	2.15 (0.74, 3.57)	0.12 (−0.24, 0.48)		1.05
10– <15	704	734	0.70 (−0.51, 1.91)	−0.03 (−0.34, 0.28)		1.03
≥15	2964	3085	0.76 (0.12, 1.39)	0.16 (−0.00, 0.33)		1.03
Bilateral oophorectomy					0.56	
No	2973	2917	1.34 (0.72, 1.95)	0.04 (−0.12, 0.20)		1.03
Yes	1938	2111	0.82 (0.06, 1.58)	0.09 (−0.11, 0.28)		1.04
Prior hormone use					0.06	
Never	2769	2769	1.56 (0.91, 2.20)	−0.10 (−0.26, 0.07)		1.03
Past	1871	1947	0.35 (−0.43, 1.13)	0.26 (0.07, 0.46)		1.03
Current	669	709	0.93 (−0.29, 2.14)	0.18 (−0.13, 0.49)		1.03
Duration of prior hormone use, yrs					0.05	
Never	2769	2769	1.56 (0.91, 2.20)	−0.10 (−0.26, 0.07)		1.03

			SBP			VVV of SBP
Subgroup	**Active (N)**	**Placebo (N)**	**Difference‡ of SBP (95%CI) at Y1**	**Difference§ of slopes (95%CI) after Y1**	**P-Fit‖**	**Ratio of VVV¶**
<5	1352	1412	−0.29 (−1.19, 0.62)	0.42 (0.19, 0.65)		1.04
5–<10	469	515	2.09 (0.62, 3.56)	0.15 (−0.22, 0.52)		1.07
≥10	720	732	0.85 (−0.38, 2.09)	−0.04 (−0.37, 0.28)		1.00
Vasomotor symptoms					0.40	
None	2962	3004	0.67 (0.04, 1.29)	0.12 (−0.04, 0.28)		1.03
Mild	1377	1441	1.35 (0.47, 2.23)	0.06 (−0.16, 0.29)		1.05
Moderate/severe	913	917	1.35 (0.24, 2.47)	−0.02 (−0.31, 0.26)		1.01
BMI, kg/m^2					0.52	
<25	1110	1096	0.44 (−0.57, 1.45)	0.05 (−0.21, 0.30)		1.05
25–<30	1798	1915	1.30 (0.52, 2.08)	0.08 (−0.12, 0.28)		1.04
≥30	2375	2385	1.11 (0.42, 1.81)	0.07 (−0.11, 0.25)		1.01
Anti-hyp. med use at baseline					0.33	
No	3108	3234	1.25 (0.69, 1.80)	0.07 (−0.07, 0.21)		1.04
Yes	2202	2195	0.68 (−0.11, 1.47)	0.06 (−0.14, 0.26)		1.02
Mean SBP at baseline, mmHg					0.18	
<120	1668	1727	0.86 (0.26, 1.47)	0.14 (−0.03, 0.31)		1.04
120–<130	1172	1268	1.78 (1.02, 2.55)	0.04 (−0.17, 0.26)		1.03
130–<140	1120	1080	0.18 (−0.69, 1.04)	0.28 (0.04, 0.53)		1.04
≥140	1350	1354	0.95 (0.06, 1.84)	−0.15 (−0.40, 0.10)		1.02
Diabetes					0.26	
No	4897	5009	1.09 (0.62, 1.57)	0.08 (−0.04, 0.20)		1.03
Yes	410	412	0.44 (−1.40, 2.29)	−0.13 (−0.61, 0.35)		1.03
Smoking					0.33	
Never	2723	2705	1.34 (0.70, 1.98)	0.05 (−0.11, 0.21)		1.05
Past	1986	2090	0.57 (−0.17, 1.32)	0.16 (−0.03, 0.36)		1.01
Current	542	571	1.74 (0.25, 3.24)	−0.22 (−0.61, 0.17)		1.04
History of CVD**					0.003	
No	4740	4870	1.32 (0.84, 1.80)	0.05 (−0.08, 0.17)		1.03
Yes	493	472	−1.54 (−3.16, 0.09)	0.32 (−0.11, 0.75)		1.02

			SBP			VVV of SBP
Subgroup	**Active (N)**	**Placebo (N)**	**Difference‡ of SBP (95%CI) at Y1**	**Difference§ of slopes (95%CI) after Y1**	**P-Fit//**	**Ratio of VVV¶**
Atrial fibrillation					0.51	
No	4959	5080	1.10 (0.62, 1.57)	0.05 (−0.08, 0.17)		1.03
Yes	246	240	0.54 (−1.77, 2.86)	0.40 (−0.20, 1.00)		1.03
Left ventricle hypertrophy					0.19	
No	4844	4962	1.17 (0.70, 1.65)	0.07 (−0.05, 0.19)		1.03
Yes	361	371	−0.04 (−2.07, 1.98)	−0.05 (−0.57, 0.47)		1.01

*The primary analysis is from a linear mixed effects (LME) model that adjusts for age, race/ethnicity, BMI and use of antihypertensive medications at baseline. The LME model includes a random intercept and random slope after year 1.

†Within-subject variability.

‡Active minus placebo (mmHg).

§Active minus placebo (mmHg/year).

//P-value for primary analysis that corresponds to an omnibus test of whether trajectories, means at Year 1 or slopes after Year 1, significantly differ between randomization groups. P-value for subgroup analysis that corresponds to an omnibus test of interaction between randomization group and subgroup.

¶Active divided by placebo.

**Includes stroke, myocardial infarction, angina, CABG and PCI.

Table 2

Effects* of CEE+MPA on Mean Systolic Blood Pressure (SBP) and Visit-to-Visit Variability (VVV†) of SBP During the Women's Health Initiative CEE +MPA Randomized Controlled Trial (n=16,608)

			SBP			VVV of SBP
Subgroup	**Active (N)**	**Placebo (N)**	**Difference‡ of SBP (95%CI) at Y1**	**Difference§ of slopes (95%CI) after Y1**	**P-Fit‖**	**Ratio of VVV¶**
Overall	**8506**	**8102**	**1.35 (0.99, 1.72)**	**0.09 (−0.03, 0.21)**	**<0.001**	**1.01**
Age, yrs					0.64	
50–54	1041	983	0.95 (0.00, 1.89)	−0.02 (−0.32, 0.27)		1.02
55–59	1796	1700	1.47 (0.73, 2.20)	0.03 (−0.21, 0.27)		1.00
60–69	3854	3655	1.22 (0.67, 1.76)	0.27 (0.09, 0.46)		1.01
70–79	1815	1764	1.71 (0.83, 2.60)	−0.20 (−0.50, 0.11)		1.01
Race/Ethnicity					0.42	
White	7141	6805	1.43 (1.03, 1.83)	0.12 (−0.02, 0.25)		1.01
Black	548	574	0.72 (−0.79, 2.22)	−0.05 (−0.56, 0.45)		1.00
Hispanic	471	415	0.28 (−1.33, 1.90)	0.12 (−0.43, 0.67)		1.04
Asian	194	169	2.63 (0.04, 5.21)	−0.16 (−1.05, 0.73)		1.08
Years since menopause					0.37	
<5	1313	1225	0.65 (−0.21, 1.50)	0.02 (−0.26, 0.31)		1.00
5–<10	1467	1486	1.43 (0.62, 2.25)	0.29 (0.01, 0.56)		1.03
10–<15	1613	1567	1.32 (0.50, 2.15)	0.27 (−0.01, 0.56)		0.98
≥15	3286	3230	1.58 (0.95, 2.20)	−0.06 (−0.28, 0.16)		1.02
Prior hormone use					0.10	
Never	6277	6022	1.41 (0.98, 1.83)	0.09 (−0.06, 0.23)		1.01
Past	1671	1587	1.43 (0.61, 2.26)	−0.07 (−0.34, 0.20)		1.00
Current	554	490	0.44 (−0.95, 1.82)	0.66 (0.20, 1.12)		1.01
Duration of prior hormone use, yrs					0.22	
Never	6277	6022	1.41 (0.98, 1.83)	0.09 (−0.06, 0.23)		1.01
<5	1539	1468	1.62 (0.78, 2.45)	0.07 (−0.21, 0.34)		1.00
5–<10	427	356	0.23 (−1.48, 1.94)	−0.04 (−0.61, 0.52)		0.98
≥10	263	255	−0.07 (−2.18, 2.05)	0.69 (−0.03, 1.42)		1.03

			SBP			VVV of SBP
Subgroup	**Active (N)**	**Placebo (N)**	**Difference‡ of SBP (95%CI) at Y1**	**Difference§ of slopes (95%CI) after Y1**	**P-Fit‖**	**Ratio of VVV¶**
Vasomotor symptoms					0.04	
None	5162	4928	1.45 (0.97, 1.93)	0.11 (−0.05, 0.27)		1.01
Mild	2190	2115	1.62 (0.92, 2.31)	0.13 (−0.10, 0.35)		1.01
Moderate/severe	1072	974	0.25 (−0.77, 1.27)	−0.09 (−0.43, 0.24)		0.97
BMI, kg/m^2					0.14	
<25	2579	2479	0.99 (0.34, 1.65)	0.30 (0.08, 0.51)		1.01
25–<30	2992	2835	1.76 (1.15, 2.37)	−0.00 (−0.21, 0.20)		1.01
≥30	2899	2737	1.22 (0.58, 1.86)	0.01 (−0.20, 0.22)		1.00
Anti-hyp. med use at baseline					0.13	
No	5994	5679	1.14 (0.73, 1.55)	0.16 (0.03, 0.29)		1.01
Yes	2512	2423	1.94 (1.18, 2.70)	−0.10 (−0.35, 0.16)		1.01
Mean SBP at baseline, mmHg					<0.001	
<120	3267	3002	0.78 (0.34, 1.21)	0.10 (−0.06, 0.26)		0.99
120–<130	1889	1879	0.98 (0.37, 1.59)	0.29 (0.06, 0.52)		1.02
130–<140	1581	1525	1.61 (0.90, 2.33)	0.10 (−0.17, 0.36)		1.04
≥140	1769	1696	2.66 (1.86, 3.45)	−0.21 (−0.51, 0.09)		1.03
Diabetes					0.48	
No	8127	7737	1.34 (0.97, 1.71)	0.11 (−0.02, 0.23)		1.01
Yes	374	360	1.48 (−0.49, 3.44)	−0.26 (−0.93, 0.41)		1.00
Smoking					0.03	
Never	4178	3999	1.72 (1.20, 2.23)	0.11 (−0.06, 0.29)		1.02
Past	3362	3157	0.95 (0.36, 1.53)	0.15 (−0.04, 0.35)		1.00
Current	880	838	1.62 (0.46, 2.78)	−0.33 (−0.72, 0.06)		1.00
History of CVD**					0.47	
No	7988	7556	1.40 (1.03, 1.78)	0.09 (−0.04, 0.21)		1.01
Yes	410	427	0.50 (−1.25, 2.26)	0.08 (−0.53, 0.69)		1.01
Atrial fibrillation					0.07	
No	8137	7744	1.30 (0.93, 1.68)	0.08 (−0.04, 0.21)		1.00
Yes	249	224	2.28 (−0.04, 4.60)	0.61 (−0.16, 1.37)		1.05

			SBP			VVV of SBP
Subgroup	**Active (N)**	**Placebo (N)**	**Difference‡ of SBP (95%CI) at Y1**	**Difference§ of slopes (95%CI) after Y1**	**P-Fit//**	**Ratio of VVV¶**
Left ventricle hypertrophy					0.42	
No	7914	7491	1.28 (0.91, 1.66)	0.12 (−0.00, 0.25)		1.00
Yes	402	432	2.35 (0.45, 4.25)	−0.30 (−0.95, 0.34)		1.08

*The primary analysis is from a linear mixed effects (LME) model that adjusts for age, race/ethnicity, BMI and use of antihypertensive medications at baseline. The LME model includes a random intercept and random slope after year 1.

†Within-subject variability.

‡Active minus placebo (mmHg).

§Active minus placebo (mmHg/year).

//P-value for primary analysis that corresponds to an omnibus test of whether trajectories, means at Year 1 or slopes after Year 1, significantly differ between randomization groups. P-value for subgroup analysis that corresponds to an omnibus test of interaction between randomization group and subgroup.

¶Active divided by placebo.

**Includes stroke, myocardial infarction, angina, CABG and PCI.