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Postmenopausal Hormone Therapy and the Risks of Coronary Heart Disease, Breast Cancer, and Stroke

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Abstract

The principal findings are briefly reviewed from the Women's Health Initiative (WHI) trials of the most commonly used postmenopausal hormone regimens in the US, conjugated equine estrogens and these same estrogens plus medroxyprogesterone acetate. A more detailed review is presented for three major clinical outcomes: coronary heart disease, the primary trial outcome for which a major benefit was hypothesized; invasive breast cancer, the primary safety outcome for which some adverse effect was expected; and stroke which surfaced as an important adverse effect with both regimens, and one that is influential in decisions concerning the continued use of postmenopausal estrogens alone. The review for these outcomes includes an update on interactions of treatment effects with study subject characteristics and exposures and with pre-randomization biomarker levels. It also includes a focus on timing issues that are important to the understanding of treatment effects. Specifically, with combined estrogen plus progestin coronary heart disease risk was elevated early with the elevation dissipating after a few years of treatment, whereas breast cancer elevations increased during the treatment period, and climbed to about a 3-fold increase following 5 years of adherence. Importantly, breast cancer risk elevations appear to be higher among women who initiate treatment at the menopause, or soon thereafter, compared to women having a longer gap time. Stroke effects, on the other hand didn't seem to vary appreciably with these timing issues. The adverse effect was evidently localized to ischemic strokes, for which there was an approximate 50% increase with either regimen. The rather limited knowledge concerning the biomarkers and biological pathways that mediate the hormone therapy effects on these diseases is also briefly reviewed.

Keywords

breast cancer; coronary heart disease; postmenopausal hormone therapy; randomized controlled trial; stroke

Introduction

The results from the Women's Health Initiative (WHI) randomized controlled trials of postmenopausal hormone therapy (HT)^{1,2} led to a major reduction in the use of these agents in the US and elsewhere. A hypothesized substantial reduction in the primary outcome, coronary heart disease (CHD), did not occur, and stroke rates were elevated, with either

0.625 mg/d conjugated equine estrogens (CEE) among women who were post-hysterectomy, or with these same estrogens plus 2.5 mg/d continuous medroxyprogesterone acetate (CEE+MPA) among women with uterus. Furthermore, breast cancer rates were substantially elevated following a few years of CEE+MPA use whereas, somewhat surprisingly, overall breast cancer rates were somewhat reduced with CEE. In conjunction with other important effects, including reductions in hip and other fracture rates with either therapy, and elevations in probable dementia especially with CEE+MPA, trial results led the judgment of unfavorable health benefits versus risks for CEE+MPA, along with more balanced health effects with CEE alone, with neither agent able to be recommended for chronic disease prevention. Both trials were stopped early, with publication of initial trial findings in 2002 for CEE+MPA,¹ and 2005 for CEE.² Subsequently there has been considerable further study of health effects of these regimens in relation to study subject characteristics, along with study of related biologic mechanisms and mediators, and longer term follow-up of trial participants has occurred. These developments will be reviewed here with an emphasis on questions that remain to be answered and needed further research.

WHI Hormone Therapy Trials: Overall Findings

WHI enrollees had the opportunity to be screened for eligibility for the HT trial, or for an overlapping trial of a low-fat dietary pattern intervention. At their one-year anniversary from randomized assignment in one or both of these clinical trial components, these women had the opportunity to be further screened for randomization into a trial of calcium and vitamin D supplementation.³ Because the hypothesized benefits of these interventions was expected to extend throughout the postmenopausal period, there was a deliberate effort to enroll women who were 70 years or older at enrollment. Table 1 shows the numbers of women by baseline age group in each of the clinical trial components. Also shown are corresponding numbers for a companion WHI Observational Study (OS), a prospective cohort study drawn from essentially the same catchment areas, and comprised of postmenopausal women who were ineligible for, or uninterested in, clinical trial participation.

Table 2, adapted from a 2007 review paper,⁴ provides summary hazard ratios and associated 95% confidence intervals (CIs) for several clinical outcomes, through the end of the HT trial intervention periods, along with pertinent citations. The big surprise, in the initial 2002 report from the CEE+MPA trial, was an elevation in CHD incidence over a 5.6-year average intervention period, in contrast to a hypothesized major risk reduction. Invasive breast cancer was the designated primary safety outcome in the HT trials, and an elevation in breast cancer incidence with CEE+MPA was observed. These risk elevations were not evident in the CEE-alone trial, over its 7.1-year average intervention period. Note, however, that stroke risk was elevated with either HT intervention, as was venous thromboembolism, especially with CEE+MPA.

At the end of the planned clinical trial intervention period (4/8/05) participating women were invited to re-consent for an additional five years of non-intervention follow-up. Summary results following several additional years of follow-up have been published for both the CEE+MPA and the CEE-alone trials.^{26,27} Most of the Table 2 HR increases or decreases dissipated within about three years of trial stoppage. Outcome specific follow-up

papers have documented an increase in breast cancer mortality²⁸ with CEE+MPA, whereas there was no hint of a reduction in colorectal cancer mortality.²⁹

Coronary Heart Disease, Breast Cancer and Stroke: Interactions and Temporal Effects

The simple HR summary statistics shown in Table 2 leave many questions unanswered: It is natural to ask how treatment effects depend on such study subject characteristics as age and the presence of disease risk factors, and on whether or not participating women had used postmenopausal hormones prior to WHI enrollment. Note, however, that the HT trials were not designed to have power for these types of subgroup analyses, and important multiple testing adjustments may be necessary to properly interpret such analyses. Another important consideration is that HT effects may depend on a number of timing issues, including time from menopause to starting HT, and duration of HT use. Furthermore, hazard ratio estimation for women who adhered to their assigned hormone or placebo pills may add valuable perspective to hormone therapy risks and benefits, even if such estimation lacks the reliability of the intent-to-treat analyses leading to Table 2.

In this section these topics will be discussed for three important clinical outcomes. CHD was the primary outcome in the HT trials, and CHD incidence was expected to be substantially reduced by either CEE or CEE+MPA on the basis of extensive preceding observational studies,³⁰ and clinical trials having cardiovascular disease risk factor outcomes.³¹ Invasive breast cancer was the designated primary safety outcome in the HT trials. An adverse effect was anticipated for both CEE and CEE+MPA.³² Also, an elevation in breast cancer risk was the trigger for the early stopping of the CEE+MPA trial.¹ Stroke surfaced as an important problem for both regimens as trial results unfolded,^{1,2} and a stroke elevation was a major motivation for the early stoppage of the CEE trial.

Beginning with CHD, defined as non-fatal myocardial infarction plus coronary death, one can note that there were surprisingly few participant characteristics or exposures that appeared to interact with the CHD hazard ratio with either CEE+MPA⁵ or CEE-alone⁶ in spite of the fact that there were, respectively, 335 and 418 CHD cases in the two trials at the time of early trial stoppage. For CEE+MPA there was a nominally significantly ($p=0.01$) higher HR among women having relatively high baseline LDL-cholesterol.⁵ For CEE there was a nominally significantly higher HR among women having relatively plasma C-reactive protein ($p=0.04$), and a suggestion (nominal $p=0.07$) of a lower HR among women who were younger (50-59 years) at randomization. However, considering the rather large number of demographic, medical, and biomarker factors considered, the predominant message is one of little evidence of CHD HR variation among participating women.

There were, however, noteworthy variations in CHD HR with years since randomization. For CEE+MPA⁵ the HRs (95% CIs) for the first, second and 6th or later years were respectively 1.81 (1.09, 3.01), 1.34 (0.82, 2.18), and 0.70 (0.42, 1.14), with a trend test significance level of 0.02. The HR trend was somewhat similar but less dramatic ($p=0.14$) for CEE⁶ with corresponding HRs (95% CIs) of 1.11 (0.64, 1.94), 1.20 (0.69, 2.10) and 0.81 (0.60, 1.10). These findings convey a picture of early elevation in risk, especially with CEE +MPA, with possible HR reversal after some years of HT use when, for example, the apparently favorable effects on blood lipids with either regimen may become relatively more

influential, and apparently unfavorable effects on inflammatory and coagulatory factors³³ relatively less so. The temporal HT patterns also provide an explanation for the optimistic reports³⁰ from observational studies on HT effects on CHD. Many of these reports had limited observation of women who were early in the course of their HT usage, so that any early risk elevations tended to be missed, and treatment effect summaries were dominated by experience following some years of HT use. In fact, WHI investigators jointly analyzed data from the HT trials, and from the WHI Observational Study, and found good agreement after accounting for time from HT initiation, for both CEE+MPA³⁴ and CEE-alone.³⁵ Note that an HR below one some years into an HT episode does not necessarily imply a risk reduction since an early risk elevation can be expected to imply a later biased HR comparison. Cumulative incidence comparisons over various follow-up periods can provide a useful adjunct to time-varying HRs for treatment effect evaluation.

The breast cancer HR patterns turned out to be equally surprising, and somewhat more complex, than those for CHD. First, even though there were more incident cases with CEE+MPA (349 invasive cancers) than with CEE-alone (237 invasive cancers), there were no nominally significant interactions of the HR with demographic, or medical history variables for CEE+MPA,¹¹ whereas nominally significant ($p<0.01$) interactions with Gail model 5-year breast cancer risk score, history of benign breast disease, and number of first degree relatives with breast cancer arose for CEE,¹² with little evidence for a breast cancer risk reduction among the high risk categories for these factors. These analyses convey the impression that the addition of MPA to the regimen may tend to overwhelm factors that may otherwise yield differential HT-associated risks.

The temporal breast cancer HR patterns are also quite interesting. The rate of invasive breast cancer diagnoses is somewhat lower with CEE+MPA compared to placebo in the first two years of use, but the cancers diagnosed were at a more advanced stage and the frequency of abnormal mammograms was considerably increased.¹¹ Subsequently the HR rises rapidly to about two^{11, 36} following 5 years of E+P use. Among women who were adherent to their assigned study pills there was a 3-fold estimated HR increase following 5 or more years of CEE+MPA use. This type of major intervention effect with CEE+MPA is consistent with breast cancer incidence patterns in the US³⁷ and elsewhere following the major reduction in the use of combined hormone therapy following the initial presentation¹ of CEE+MPA trial results. Specifically, one can project that this change in clinical practice has resulted in 15,000-20,000 fewer invasive breast cancers each year since 2002 in the US alone.

Temporal HR patterns were not evident with CEE-alone, with its suggestive evidence ($p=0.09$) for a breast cancer risk reduction. There was stronger evidence for risk reduction ($p=0.03$) among women who adhered to their assigned study pills.¹² A breast cancer risk reduction with CEE was unanticipated, given a wealth of observational data suggesting a risk elevation of about 30%.³² Also, an overall HR estimate of 1.24 with CEE+MPA seems small relative to an approximate 2-fold increase arising from observational data sources.³² The latter discrepancy is somewhat explained by the HR pattern with increasing duration of use described in the preceding paragraph, but significantly higher HRs arose from the WHI OS than from the HT trials for both CEE+MPA³⁸ and CEE³⁹ following detailed control for eligibility factors, potential confounding factors, for mammography utilization, and for

duration of HT use. Evidently some other factor was needed in the analyses for agreement between the WHI clinical trials and observational study. A clue to such factor is obtained by noting that much of the data in support of a breast cancer risk elevation in the CEE+MPA trial arose from women who had used postmenopausal hormones prior to randomization,¹¹ whereas much of the support for a risk reduction with CEE-alone arose from women who had not used hormone therapy prior to trial enrollment. As is typical in community use of these regimens, women who had used hormone therapy prior to trial enrollment had mostly begun at the menopause or within a few years thereafter, whereas most HT trial enrollees who were without prior HT use were many years past the menopause at enrollment. This occurred in both trials, but especially in the CEE-alone trial. This observation suggested another time variable; namely, time from menopause to first use of HT, or 'gap' time as an additional factor to consider. Upon doing so HRs from the WHI HT trials and OS gave breast cancer HRs in good agreement, for both CEE+MPA³⁸ and CEE-alone.³⁹ Combined HT trial and OS data analyses⁴⁰ led to estimated HRs (95% CIs) for adherent women who begin CEE+MPA at the menopause of 1.05 (0.56, 1.97), 2.18 (1.31, 3.63), and 3.15 (1.90, 5.20) in duration of use categories of 0-2, 2-5 and 5 or more years respectively. Corresponding HRs (95% CIs) for CEE-alone were 1.44 (0.54, 3.84), 1.15 (0.57, 2.32) and 1.00 (0.54, 1.84). These analyses do not support a breast cancer risk reduction among women who begin CEE at or soon after the menopause, whereas they do support a major risk elevation among such women after a few years of CEE+MPA use. For both regimens there was clear evidence of smaller HRs with longer times from menopause to first use of HT, perhaps reflecting a differential response of mammary epithelial cells to these agents, after the breast involution that follows the menopause. Higher breast cancer HRs among women having relatively short gap times has recently been found in other observational studies, including in the Million Women Study for both CEE+MPA and CEE-alone.⁴¹

For stroke, as shown in Table 2, there was an estimated overall risk increase of about 30% with either CEE+MPA or CEE-alone, with stroke diagnosed for 258 and 295 women in the respective trials.^{7,8} This increase was entirely in the ischemic stroke category, which comprised about 80% of diagnosed strokes in each trial. The intent-to-treat HRs (95% CIs) for ischemic stroke were 1.44 (1.09, 1.90) for CEE+MPA, and 1.55 (1.19, 2.01) for CEE alone. Stroke HRs did not show any clear HR patterns with duration of use, for either regimen. Moreover, there were no demographic or medical factors studied that interacted with the stroke HRs for either CEE+MPA⁷ or CEE-alone.⁸ Also the same set of inflammation, coagulation and thrombosis factors as was considered for CHD was also studied for stroke in a nested case-control study, and no factors considered interacted significantly with stroke HR for either hormone therapy regimen.^{7,8,42} Combined HT trial and OS analyses were also considered for stroke, but HRs were significantly lower from the OS than from the clinical trials, and this discrepancy was not explained by control for available confounding factors, or by timing issues related to HT usage patterns.^{34,35,40}

For both breast cancer and stroke additional studies have been reported that examine evidence for an interaction of hormone therapy hazard ratios with single nucleotide polymorphisms (SNPs). For either disease several thousand SNPs showing some potential for disease association were selected, and interactions with clinical trial treatment effects were evaluated in efficient case-only analyses that are justified by the independence of

genotype and randomization assignment. For breast cancer a particular SNP (rs3750817) in intron 2 of the fibroblast growth factor receptor two (FGFR2) gene on chromosome 10, where a strong breast cancer risk signal was known to reside, showed evidence of interaction with HRs for both CEE and CEE+MPA. Women homozygous for the minor allele of this SNP had reduced breast cancer risk, and relatively more favorable HRs with either CEE or CEE+MPA.⁴³ Interaction with the CEE HR was also suggested for a SNP(rs7705343) in the mitochondrial ribosomal protein S30 (MRPS30) region of chromosome 5, with evidence for a risk reduction with CEE deriving mainly from women who were minor allele homozygous for this SNP.⁴⁴ For stroke, an interaction of the CEE+MPA HR was suggested for a SNP in coagulation Factor XIII subunit A (F13A1) region of chromosome 6 a clotting factor XIII SNP on chromosome, and interactions with both the CEE+MPA and CEE HRs were suggested for a SNP in the proprotein convertase subtilisin kexin 9 (PCSK9) region of chromosome 1.⁴⁵ These findings require confirmation, but they have the potential to identify subsets of women for whom adverse effects in relation to these diseases are not apparent. Additional studies of this type are continuing involving a larger number of SNPs for each of the diseases highlighted in this paper.

Coronary Heart Disease, Breast Cancer and Stroke: Mechanisms and Mediators

In addition to the study of overall hormone therapy effects, and interactions with study subject characteristics and exposures it is important to consider HT effects on biological intermediaries, and to try to identify which of the changes in intermediate variables seems to be responsible for observed effects. This latter type of analysis, sometimes referred to as mediation analyses is considerably more challenging than analyses to identify interactions, for statistical reasons: interacting baseline variables are typically orthogonal to treatment assignments on the basis of randomized treatment assignments, whereas relevant changes in mediating variables may be highly correlated with treatment assignment. If this correlation is coupled with measurement error in potential mediating variables it may take specialized methods to identify the important mediators and biological mechanisms. The principal idea of a mediation analysis is to examine the extent to which a treatment effect can be explained by including post-randomization change in the potential mediator in HR analyses.

As mentioned above nested case-control studies took place in the context of the HT trials with a principal goal of identifying biomarker mediators of CEE and CEE+MPA effects on key clinical outcomes, with biomarkers measured at baseline and 1-year following randomization. For CHD³³ and stroke⁴² this case-control study focused on plasma lipids and lipoproteins, and on inflammatory and coagulation/thrombosis factors. As was known from preceding research,³¹ these regimens, especially CEE-alone, have a substantial favorable impact on HDL and LDL cholesterol. They also both have similar and noteworthy adverse effects on inflammatory factors, including an elevation in C-reactive protein of about 60%, and several coagulation factors were also impacted. However, post-treatment changes in these biomarkers individually did not show an ability to appreciably explain CEE or CEE +MPA effects on these diseases.^{33,42} These analyses should not be regarded as providing evidence against the importance of the factors and pathways considered in relation to hormone therapy effects on CHD and stroke. Specifically, the mediation analyses focus on post 1-year treatment effects, whereas much of the evidence for an elevation in CHD risk

pertained to the first, or at least early, years of use. Also, the regimens under study involved a biomarker changes that appear to be both favorable and unfavorable, including favorable effects on lipoprotein cholesterol levels and unfavorable effects on inflammatory and coagulation factors. It may be necessary to consider favorable and unfavorable biomarker changes jointly in an attempt to explain temporal HR patterns for CEE and CEE+MPA. Even then, the aforementioned biomarker measurement error issue may be a major stumbling block in identification of the key biological pathways.

For breast cancer the biomarker studies to date have focused on serum sex hormone changes⁴⁶. Changes from baseline to 1-year for serum estrogens were very similar for CEE and for CEE+MPA, and were quite substantial: 2 to 3-fold increases in estradiol, 2-fold increase in free estradiol, and an impressive 3 to 4-fold increase in estrone. There was also a, presumably opposing, approximate 2.5-fold increase in sex hormone binding globulin. A modest reduction in serum progesterone was also observed following CEE+MPA use.⁴⁶ Though yet unpublished, there is reason to think that the effect of both regimens on breast cancer risk can be substantially explained by the magnitude of a woman's serum sex hormone response to hormone therapy, especially after taking a suitable account of measurement error in the blood hormone assessments. Clearly, another factor related to MPA must also be influential, given the quite different overall HRs for CEE-alone versus CEE+MPA.

A proteomic discovery study was also undertaken in hope of novel insight into the biological effects of HT, and their mediation potential. Using an intact protein analysis system that reliably identifies and quantifies relative protein abundance for about 300-400 proteins, it was found^{47,48} that there was nominally significant evidence of change between baseline and 1-year in blood concentrations of nearly half of the proteins quantified for women assigned to active hormone therapy.⁴⁸ This observation alone may suggest that a cautious approach is needed in the use of these potent regimens. Changes were found in many pathways that may be relevant to observed clinical effects of HT, including inflammation, coagulation, metabolism, osteogenesis, immune response, and growth factors. Moreover, the quantitative changes were quite similar between CEE and CEE+MPA. The same proteomic platform was also applied to case-control data from the OS, to help identify the proteins that may be relevant to the risk of CHD, stroke and breast cancer. This led to the identification of several proteins that also were affected by hormone therapy, for both CHD and stroke.⁴⁹ For example, beta 2 microglobulin was associated with CHD risk, and also elevated by both CEE and CEE+MPA. Similarly insulin-like growth factor binding protein 4 was associated with stroke risk, and elevated by both regimens. The association of these risk markers with CHD and stroke were then confirmed in case-control analyses in the HT trial cohorts, and the mediation potential of these and selected other highly ranked protein candidates are currently being evaluated in case-control studies the HT trial setting.

Summary and Needed Further Research

Though much has been learned through the conduct of the WHI HT trials, and the changes in clinical practice and public health impact that followed trial results are major, there remains much to be learned concerning the biological pathways and health effects of the

regimens tested. Furthermore, research is needed toward the development of approaches to manage vasomotor symptoms among postmenopausal women, without unfavorable health consequences.

More specifically, even though there was good reason to design the HT trials to obtain disease prevention information across a broad postmenopausal age range for regimens which were used by about 8 million (CEE) and 6 million (CEE+MPA) women in the US alone, at the time these trials were planned. However, health risks versus benefits turned out to be somewhat less favorable among older postmenopausal women, who are no longer likely to consider these preparations for chronic disease prevention, whereas WHI data are less comprehensive than desirable among younger postmenopausal women who are experiencing menopausal symptoms and making decisions about HT use. Hence HT trial analyses need some qualification when applied to this important subsets, though we have been able to bring in OS data in an unrestricted manner to mitigate this limitation to some degree. Also, there are important questions related to the effects of altered dose or schedule of the agents tested, and concerning the effects of other hormone therapy regimens including transdermal rather than oral preparations that could, for example, be hypothesized to avoid some adverse cardiovascular effects related to first-pass hepatic metabolism. Similarly, analyses to date on circulating blood hormones and their relationship to CEE and, especially, CEE+MPA effects on breast cancer suggest that regimens be sought having reduced impact on estrone and estradiol, while still providing symptom control. Of course, impact on each of the outcomes listed in Table 2 among other outcomes would need to be considered in the development and evaluation of other hormone therapy preparations and regimens. It follows that much high priority research remains to be accomplished in the hormone therapy area, which continues to be of great medical and public health importance.

Note added in proof: Since the time of completion of this manuscript, WHI investigators have presented⁵⁰ a rather comprehensive analysis of data from both HT trials with extended post-stopping trial follow-up. The reader is referred to this paper for additional data analyses, especially for outcomes other than the three focused on here.

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Table 1
Women's Health Initiative sample sizes (% of total) by age group

Age group	Dietary modification	HT-With uterus (CEE+MPA ^a)	HT-without uterus (CEE ^a)	Calcium and vitamin D	Observational study
50-54	6,961 (14)	2,029 (12)	1,396 (13)	5,157 (14)	12,386 (13)
55-59	11,043 (23)	3,492 (21)	1,916 (18)	8,265 (23)	17,321 (18)
60-69	22,713 (47)	7,512 (45)	4,852 (45)	16,520 (46)	41,196 (44)
70-79	8,118 (17)	3,575 (22)	2,575 (24)	6,340 (17)	22,773 (24)
Total	48,835	16,608	10,739	36,282	93,676

^a Abbreviations: HT, postmenopausal hormone therapy; CEE, conjugated equine estrogens; CEE+MPA, conjugated equine estrogens plus medroxyprogesterone acetate

Table 2

Hazard ratios (HR) and 95% confidence intervals (CIs) for various clinical outcomes in the CEE+MPA and CEE-alone trials.^a

	Hypothesized effect	CEE+MPA			CEE-alone		
		HR	95% CI	AR	HR	95% CI	AR
CHD ^{5,6}	↓	1.24	1.00--1.54	+6	0.95	0.79--1.15	-3
Stroke ^{7,8}	↔↓	1.31	1.02--1.68	+8	1.37	1.09--1.73	+12
PE ^{9,10}	↑	2.13	1.45--3.11	+10	1.37	0.90--2.07	+4
VTE ^{9,10}	↑	2.06	1.57--2.70	+18	1.32	0.99--1.75	+8
Breast cancer ^{11,12}	↑	1.24	1.02--1.50	+8	0.80	0.62--1.04	-6
Colorectal cancer ^{13,14}	↓	0.56	0.38--0.81	-7	1.08	0.75--1.55	+1
Endometrial cancer ¹⁵		0.81	0.48--1.36	-1	NA		
Hip fractures ^{16,17}	↓	0.67	0.47--0.96	-5	0.65	0.45--0.94	-7
Total fractures ^{16,17}	↓	0.76	0.69--0.83	-47	0.71	0.64--0.80	-53
Total mortality ^{1,2}	↓	0.98 ^c	0.82--1.18	-1	1.04 ^c	0.91--1.12	+3
Global index ^{1,2}		1.15 ^c	1.03--1.28	+19	1.01 ^c	1.09--1.12	+2
Diabetes ^{18,19}		0.79	0.67--0.93		0.88	0.77--1.01	
Gall bladder dis ²⁰	↑	1.59	1.28--1.97		1.67	1.35--2.06	
Stress incontinence ²¹		1.87	1.61--2.18		2.15	1.77--2.62	
Urge incontinence ²¹		1.15	0.99--1.34		1.32	1.10--1.58	
PAD ^{22,23}		0.89	0.63--1.25		1.32	0.99--1.77	
Probable dement ^{24,25}	↓	2.05	1.21--3.48		1.49	0.83--2.66	

^a Abbreviations: AR, attributable risk per 10,000 person years; CEE+MPA, estrogen plus progestin; CEE-alone, estrogen alone; HR, hazard ratio; CI, confidence interval. Hazard ratio estimates are based on proportional hazards analysis stratified by age (five-year categories) and randomization in the dietary modification trial; PE, pulmonary embolism; VTE, venous thromboembolism; PAD, peripheral artery disease

^b Global index defined for each woman as the time to the earliest diagnosis of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (for E+P), hip fractures, and death from other causes.

^c Based on an average 5.2 and 6.8 years of follow-up for E+P and E-alone, respectively. All others based on an average of 5.6 (CEE+MPA) and 7.1 (CEE-alone) years of follow-up.