Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

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Context The timing of initiation of hormone therapy may influence its effect on cardiovascular disease.

Objective To explore whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause began.

Design, Setting, and Participants Secondary analysis of the Women's Health Initiative (WHI) randomized controlled trials of hormone therapy in which 10 739 postmenopausal women who had undergone a hysterectomy were randomized to conjugated equine estrogens (CEE) or placebo and 16 608 postmenopausal women who had not had a hysterectomy were randomized to CEE plus medroxyprogesterone acetate (CEE + MPA) or placebo. Women aged 50 to 79 years were recruited to the study from 40 US clinical centers between September 1993 and October 1998.

Main Outcome Measures Statistical test for trend of the effect of hormone therapy on coronary heart disease (CHD) and stroke across categories of age and years since menopause in the combined trials.

Results In the combined trials, there were 396 cases of CHD and 327 cases of stroke in the hormone therapy group vs 379 cases of CHD and 239 cases of stroke in the placebo group. For women with less than 10 years since menopause began, the hazard ratio (HR) for CHD was 0.76 (95% confidence interval [CI], 0.50-1.16); 10 to 19 years, 1.10 (95% CI, 0.84-1.45); and 20 or more years, 1.28 (95% CI, 1.03-1.58) (*P* for trend = .02). The estimated absolute excess risk for CHD for women within 10 years of menopause was –6 per 10 000 person-years; for women 10 to 19 years since menopause began, 4 per 10 000 person-years; and for women 20 or more years from menopause onset, 17 per 10 000 person-years. For the age group of 50 to 59 years, the HR for CHD was 0.93 (95% CI, 0.65-1.33) and the absolute excess risk was –2 per 10 000 person-years; 60 to 69 years, 0.98 (95% CI, 0.79-1.21) and –1 per 10 000 person-years; and 70 to 79 years, 1.26 (95% CI, 1.00-1.59) and 19 per 10 000 person-years (*P* for trend = .16). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12-1.56). Risk did not vary significantly by age or time since menopause. There was a nonsignificant tendency for the effects of hormone therapy on total mortality to be more favorable in younger than older women (HR of 0.70 for 50-59 years; 1.05 for 60-69 years, and 1.14 for 70-79 years; *P* for trend = .06).

Conclusions Women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance. A similar nonsignificant trend was observed for total mortality but the risk of stroke was elevated regardless of years since menopause. These data should be considered in regard to the short-term treatment of menopausal symptoms.

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In observational studies of women with and without existing coronary heart disease (CHD), the use of postmenopausal hormone therapy is associated with a reduced risk of CHD events.[1] In contrast, clinical trials have shown no benefit and some trials have suggested an increased risk of CHD during the first year after randomization.[2,3] The Women's Health Initiative (WHI) reported a hazard ratio (HR) for CHD of 0.95 (95% confidence interval [CI], 0.70-1.16) in the trial of conjugated equine estrogens (CEE) and an HR of 1.24 (95% CI, 1.00-1.54) in the trial of CEE plus medroxyprogesterone acetate (CEE + MPA).[3,4] While observational studies have evidently overestimated benefit due to confounding, selection biases, and other limitations,[5,6] an additional source of discrepancy may be the timing of initiation of hormone therapy in relation to the underlying state of the vasculature. Some investigators have hypothesized

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that estrogen may delay the onset of the earliest stages of atherosclerosis, which are more likely to be present in younger women, but it may be ineffective or even trigger events in the presence of existing advanced lesions such as those found in older women.[7] The potential existence of a window of opportunity to reduce cardiovascular disease is supported by animal and laboratory studies.[6]

Compared with observational studies of hormone therapy use among healthy women such as the Nurses' Health Study, most women in the randomized hormone trials were older and the majority commenced study hormones more than a decade after menopause began.[3,4,8] Subgroup analyses in the 2 WHI trials of hormone therapy suggested a nonsignificant reduction in risk of CHD in women aged 50 to 59 years in the trial of CEE[4] or in women with less than 10 years since menopause in the trial of CEE + MPA.[3] Risk of stroke did not appear to be reduced in these subgroups.[9,10] The numbers of events in the subgroups in the individual trials were too small to provide definitive answers but the similar direction of the findings supports the idea that pooling the trials could yield clearer answers.

In this secondary analysis, statistical power was improved by the use of techniques that allow combining the trial data to examine trends in the effects of hormone therapy on CHD and stroke across categories of age and years since menopause. These results could apply to a population similar to the women enrolled in the WHI trials, which included 40% of women taking unopposed estrogen (CEE) or placebo and 60% of women taking estrogen plus progestin (CEE + MPA) or placebo. Total mortality and a predefined global index were examined to capture the overall effects of hormone therapy on disease outcomes. Combined hormone therapy trial analyses and subgroup analyses by age were prespecified in the WHI protocol; other analyses were not prespecified. The subgroup and secondary analyses are exploratory; however, given that these are the best available data, the potential clinical implications of our findings also are examined.

METHODS

Study Participants and Outcomes

The WHI trials enrolled 27 347 predominantly healthy postmenopausal women aged 50 to 79 years from September 1993 to October 1998 at 40 US clinical centers based on hysterectomy status. Of these women, 10 739 had undergone a hysterectomy and were randomized to 0.625 mg/d of CEE or placebo and 16 608 had not had a hysterectomy and were randomized to 0.625 mg/d of CEE plus 2.5 mg/d of MPA or placebo. Details have been published elswhere.[11,12]

The trials were reviewed and approved by the institutional review boards at each clinical center and all participants provided written informed consent. All outcomes were centrally adjudicated. The main outcomes for the current analyses were CHD (defined as nonfatal myocardial infarction, CHD death, or silent myocardial infarction) and stroke. Other outcomes were mortality and a global index (defined as the first occurrence of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer [CEE + MPA trial only], hip fracture, or death from other causes) used for trial monitoring. Clinical events that were self-reported by participants prior to unblinding at trial closure and subsequently adjudicated were included. Due to the compressed timeline for the initial publications,[3,11] 13 additional adjudicated cases each of CHD and stroke from the CEE + MPA trial were available for this analysis.

Statistical Analysis

Age at menopause was defined by the age at which a woman last had any menstrual bleeding, bilateral oophorectomy, or began using menopausal hormone therapy. For hysterectomy without bilateral oophorectomy, the age at menopause was the age at which a woman either began using hormone therapy or first had vasomotor symptoms (ie, hot flashes, night sweats). For women who had a hysterectomy without bilateral oophorectomy at age 50 years or older but no use of hormone therapy or symptoms, the age at menopause was defined as the age when the hysterectomy was performed. If the algorithm defined an age at menopause as older than 60 years, it was recoded as 60 years. Any misclassification of age at menopause is likely to be nondifferential and would tend to bias the results toward the null. Age at menopause could not be defined (due to missing values) in 1420 (8.5%) women who had not had a hysterectomy and in 1610 (15%) women who had a hysterectomy. These women were excluded from the years since menopause analyses, which included 24 317 participants.

Study participants completed a questionnaire at baseline that included a probe for the presence of vasomotor symptoms (hot flashes or night sweats) during the prior 4 weeks. If present, participants were asked how bothersome the symptom was. Mild indicated that the symptom did not interfere with usual activities; moderate, the symptom interfered somewhat with usual activities; and severe, the symptom was so severe that usual activities could not be performed.

Event rate comparisons were based on the intent-to-treat principle using failure time methods. For a given outcome, the time to event was the number of days from randomization to the first diagnosis of the designated event. Comparisons of outcomes are presented as HRs and 95% CIs stratified by prior cardiovascular disease (defined as history of myocardial infarction, angina, coronary or carotid revascularization, stroke, transient ischemic attack, or peripheral arterial disease) and randomization status in the Dietary Modification Trial. The stratified models allow for flexible (and possibly different) hazard functions between strata and hence more accurately capture the effects of hormone therapy. Preliminary analyses

showed no striking differences in HRs across categories of age or years since menopause in women with and without prior cardiovascular disease, or in unadjusted models and models adjusted for baseline risk factors (race/ethnicity, education, physical activity, prior hormone use, body mass index [calculated as weight in kilograms divided by height in meters squared], left ventricular hypertrophy by electrocardiographic criteria, current smoking, hypertension, treated diabetes, and treated high serum cholesterol level). Therefore, the results of unadjusted models for all women are presented. For consistency with the display of HRs within categories of age or years since menopause, the estimated absolute excess risks were obtained by applying the HR in each category to the observed annualized incidence in the placebo group. The 95% CIs were calculated by bootstrap methods. Likelihood ratio tests were used to test for differences between the age categories and the categories for years since menopause.

The primary analyses of this study were based on the 2 trials combined. Separate tests for trend were performed to examine differences in hormone effects across 3 preselected, coded categories of age (50-59, 60-69, 70-79 years) or years since menopause (<10, 10-19, and ≥20) using Cox regression model interaction terms.[13] The tests stratified the baseline disease rates for the CEE and CEE + MPA cohorts by active vs placebo (4 strata), while leaving the form of the (marginal) HR for hormone therapy unspecified as a function of time from randomization. The marginal HR dependence on age or years since menopause also was unrestricted through the separate inclusion for each trial cohort of indicator variables for the upper 2 age group categories or years since menopause categories in the log HR models.

The models included regression terms for interaction between cohorts and coded indicator variables for the 3 categories of age or years since menopause. The categories were assigned an ordinal number (1, 2, 3) and then the resulting variable was fitted as a continuous linear variable in the risk models. Interaction terms between age or years since menopause and active vs placebo groups tested whether there were differential effects of hormone therapy as a function of age or years since menopause. These models allow the data for the 2 trials to be combined because they do not make assumptions about baseline risk or the overall treatment effect of hormone therapy in each of the trials. Analyses also were performed for each of the trials separately. The method used to test HR interactions differs slightly from that used in previous publications,[3,4,12] in that age and years since menopause are modeled as coded rather than as continuous variables. Models using coded variables are likely to be less sensitive to the effects of extreme values but may occasionally yield different results than the models using continuous variables.

Other analyses were defined for the purposes of this study based on a priori considerations of biologic plausibility. These included analyses aimed at separating out the effects of age and years since menopause by including terms for both variables as well as an interaction term. Models allowing the HRs and baseline disease incidence to vary by risk factor status were used to directly compare the HRs between the 2 trials. Further analyses tested whether the trends in the effect of hormone therapy by age or years since menopause varied with several factors potentially related to hormone status (eg, prior hormone use [never, past, current]; oophorectomy; presence or absence of vasomotor symptoms [never, mild, moderate or severe] at baseline). Tests were performed by including appropriate additional product interaction terms (eg, 3-way interaction of vasomotor symptoms, age, and hormone therapy treatment effect). The possibility that interactions between age and years since menopause could vary by duration of hormone therapy was examined in models and included additional product terms for duration of therapy. Adherence-adjusted sensitivity analyses censored a woman's event history 6 months after becoming nonadherent (defined as taking <80% of study drugs or completely stopping use). Analyses of the effects of hormone therapy also were performed by years since last exposure to either endogenous or exogenous hormones (years since menopause or last use of hormone therapy).

Statistical tests were undertaken at the .01 level to partially account for multiple testing issues and the post hoc nature of some of the tests. Forty-two tests for trend, 33 additional interaction tests, and 62 comparisons of HRs were performed (a total of 137 tests). Two *P* values were significant (1-2 were expected by chance). For consistency with previous WHI studies, HRs and 95% CIs were used. An HR of less than 1 favored hormone therapy and greater than 1 favored placebo. The 95% CIs were estimated in 182 subgroups. Of these 182, 19 did not include 1 (9 were expected by chance). Statistical analyses were performed using SAS version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

As previously reported, women in the CEE trial had a more adverse cardiovascular risk profile than women in the CEE + MPA trial, with a higher prevalence of obesity, left ventricular hypertrophy by electrocardiogram, hypertension, diabetes, hypercholesterolemia, and prior history of cardiovascular disease.[3,4,9-12] Previous use of postmenopausal hormones was reported by 61% and 41% of women with and without a prior bilateral oophorectomy, respectively, in the CEE trial compared with 26% of women who had not had a hysterectomy in the CEE + MPA trial. Vasomotor symptoms were reported in 43% (17% moderate or severe) of CEE participants and 38% (12% moderate or severe) of CEE + MPA participants, and were more frequent in women who initiated therapy closer to the onset of

menopause (TABLE 1 and TABLE 2). Coronary risk factors (except smoking) and prior cardiovascular disease increased markedly with increasing age and years since menopause (data not shown).

Overall Effects of Hormone Therapy (All Participants)

Consistent with previous WHI studies,[3,4] hormone therapy did not reduce overall risk of CHD (TABLE 3). As before, the HR for CHD was lower when participants were taking CEE than when taking CEE + MPA (0.95 vs 1.23; $P = .02$ after adjusting for risk factors).[4] Risk of stroke was increased (HR, 1.32; 95% CI, 1.12-1.56) in the combined trials, with no difference between the individual trials. Individual trial results were similar to those described in previous publications using centrally coded data.[3,4,9,10,12] Estimated absolute excess risks per 10 000 person-years were approximately 3 for CHD, 9 for stroke, 1 for total mortality, and 14.5 for the global index in the combined trials, under a constant HR model for each trial.

Effects of Hormone Therapy by Age at Randomization

The numbers of events increased with increasing age but there was no statistically significant additional effect of hormone therapy by age for any outcome in the combined trials (TABLE 4). The trends in HRs for CHD appeared to be somewhat more pronounced in women without prior cardiovascular disease with HRs of 0.91, 0.97, and 1.33 across the 3 age groups (535 cases; P for trend = .10) compared with 0.99, 0.98, and 1.12 in women with prior cardiovascular disease

Table 1. Selected Baseline Characteristics of Participants in the Trial of Conjugated Equine Estrogens (CEE) (n = 10 739)*

	No. (%) of Participants							
	Randomization Assignment		Age at Randomization			Years Since Menopause		
	CEE (n = 5310)	Placebo (n = 5429)	50-59 y (n = 3310)	60-69 y (n = 4852)	70-79 y (n = 2577)	<10 (n = 1643)	10-19 (n = 2936)	≥20 (n = 4550)
Years since menopause								
<10	826 (15.6)	817 (15.0)	1237 (37.4)	406 (8.4)	0			
10-19	1436 (27.0)	1500 (27.6)	1030 (31.1)	1564 (32.2)	342 (13.3)			
≥20	2231 (42.0)	2319 (42.7)	524 (15.8)	2150 (44.3)	1876 (72.8)			
Age group, y								
50-59						1237 (75.3)	1030 (35.1)	524 (11.5)
60-69						406 (24.7)	1564 (53.3)	2150 (47.3)
70-79						0	342 (11.6)	1876 (41.2)
Vasomotor symptoms								
None	2962 (55.8)	3004 (55.3)	1245 (37.6)	2850 (58.7)	1871 (72.6)	770 (46.8)	1834 (62.4)	3067 (68.9)
Mild	1377 (25.9)	1442 (26.6)	1132 (34.2)	1243 (25.6)	444 (17.2)	531 (32.3)	686 (23.3)	955 (21.4)
Moderate or severe	913 (17.2)	917 (16.9)	903 (27.3)	706 (14.6)	221 (8.6)	342 (20.8)	416 (14.1)	528 (11.8)
Prior use of hormone therapy								
Never	2769 (52.1)	2770 (51.0)	1671 (50.5)	2498 (51.5)	1370 (53.2)	835 (50.8)	1383 (47.1)	1711 (37.6)
Past	1871 (35.2)	1948 (35.9)	935 (28.2)	1247 (36.0)	626 (24.3)	452 (27.5)	1036 (35.3)	2331 (51.2)
Current	669 (12.6)	708 (13.0)	359 (18.0)	603 (12.4)	389 (15.1)	356 (21.7)	516 (17.6)	505 (11.1)
Duration of prior hormone therapy use, y								
<5	1352 (25.5)	1412 (26.0)	935 (28.2)	1203 (24.8)	626 (24.3)	579 (35.2)	786 (26.8)	1399 (30.7)
5-9	469 (8.8)	515 (9.5)	359 (10.8)	433 (8.9)	192 (7.5)	223 (13.6)	295 (10.0)	466 (10.2)
≥10	720 (13.6)	732 (13.5)	345 (10.4)	718 (14.8)	389 (15.1)	6 (0.4)	472 (16.1)	974 (21.4)
Prior bilateral oophorectomy								
No	2973 (56.0)	2917 (53.7)	2006 (60.6)	2578 (53.1)	1306 (50.7)	1216 (74.0)	1473 (50.2)	1816 (39.9)
Yes	1938 (36.5)	2111 (38.9)	1128 (34.1)	1904 (39.2)	1017 (39.5)	334 (20.3)	1279 (43.6)	2431 (53.4)
Hormone therapy use among participants with bilateral oophorectomy								
Never	737 (38.0)	829 (39.3)	352 (31.2)	755 (39.7)	459 (45.1)	104 (31.1)	537 (42.0)	920 (37.8)
Past	894 (46.1)	968 (45.9)	508 (45.0)	870 (45.7)	484 (47.6)	132 (39.5)	491 (38.4)	1239 (51.0)
Current	307 (15.8)	313 (14.8)	268 (23.8)	278 (14.6)	74 (7.3)	98 (29.3)	250 (19.5)	271 (11.2)
Hormone therapy use among participants without bilateral oophorectomy								
Never	1783 (60.1)	1699 (58.2)	1209 (60.3)	1525 (59.2)	752 (57.6)	679 (55.8)	755 (51.3)	667 (36.7)
Past	861 (29.0)	857 (29.4)	485 (24.1)	767 (29.8)	466 (35.7)	298 (24.5)	477 (32.4)	943 (51.9)
Current	324 (10.9)	359 (12.3)	312 (15.6)	283 (11.0)	88 (6.7)	239 (19.7)	241 (16.4)	203 (11.1)

*The numbers may not add up to the total because of missing data.

(214 cases; *P* for trend=.72); however, these trends did not differ significantly (*P* for interaction=.54). There were no significant increases in risk due to hormone therapy for any outcome at ages 50 to 59 years, but increases in risk for CHD, stroke, and global index events in some older age categories were noted. There was a reduction in total mortality in the age group of 50 to 59 years (HR, 0.70; 95% CI, 0.51-0.96), with a nonsignificant trend for increasing HRs across age groups (*P*=.06). In adjusted models, the HRs of CHD (*P*=.04) and global index events (*P*=.04) were nonsignificantly lower in the age group of 50 to 59 years for women taking CEE compared with women taking CEE+MPA but HRs were comparable at older ages (results not shown). The HR for the global index increased with age in the CEE trial (*P* for trend=.01). However, the trend statistics for CHD and global index did not differ between the trials.

Effects of Hormone Therapy by Years Since Menopause

The HR for CHD was 0.76 in women with less than 10 years since menopause, 1.10 for women with 10 to less than 20 years since menopause, and 1.28 for women with more than 20 years since menopause (*P* for trend=.02; TABLE 5). Hormone therapy increased the risk of CHD in women with 20 or more years since menopause (HR, 1.28; 95% CI, 1.03-1.58). In women without prior cardiovascular disease, the HRs across categories of years since menopause were 0.78, 1.10, and 1.35 (464 cases; *P* for trend=.02) and in women with prior cardiovascular disease they were 0.59, 1.08, and 1.14 (180 cases; *P* for trend=.44); these trends did not differ significantly (*P* for interaction=.68). In contrast to CHD, the effect of hormone therapy on stroke risk was similar in all categories of years since menopause, with a HR of 1.77 (95% CI, 1.05-2.98) in women with less than 10 years since menopause. In women with less than 10 years since menopause without prior cardiovascular disease, the HR for stroke was 1.64; after excluding women older than 60 years, the HR attenuated to 1.23 (all 95% CIs included 1). There were no significant differences in the HRs between the trials in any category of years since menopause in the adjusted models (results not shown), and the trend statistics for treatment effects by years since menopause also were similar for all outcomes.

Estimated Absolute Excess Risk

The combination of low incidence rates and modest HRs at ages 50 to 59 years led to low or no absolute excess risks of CHD, stroke, total mortality, or global index events due to hormone therapy in that age group (FIGURE 1). With increasing age, the higher incidence rates and larger HRs yielded progressively larger estimated absolute excess risks due to hormone therapy. At ages 50 to 59 years, there were 10 fewer deaths per 10 000 person-years compared with 16 additional deaths at ages 70 to 79 years

Table 2. Selected Baseline Characteristics of Participants in the Trial of Conjugated Equine Estrogens Plus Medroxyprogesterone Acetate (CEE + MPA) (n = 16 608)*

	No. (%) of Participants							
	Randomization Assignment		Age at Randomization			Years Since Menopause		
	CEE + MPA (n = 8506)	Placebo (n = 8102)	50-59 y (n = 5522)	60-69 y (n = 7510)	70-79 y (n = 3576)	<10 (n = 5494)	10-19 (n = 6041)	≥20 (n = 3653)
Years since menopause								
<10	2782 (32.7)	2712 (33.5)	4092 (74.1)	1402 (18.7)	0			
10-19	3947 (35.8)	2994 (37.0)	831 (15.0)	4320 (57.5)	890 (24.9)			
≥20	1850 (21.7)	1803 (22.3)	55 (1.0)	1145 (15.2)	2453 (68.6)			
Age group, y								
50-59						4092 (74.5)	831 (13.8)	55 (1.5)
60-69						1402 (25.5)	4320 (71.5)	1145 (31.3)
70-79						0	890 (14.7)	2453 (76.2)
Vasomotor symptoms								
None	5162 (60.7)	4928 (60.8)	2298 (41.6)	4974 (66.2)	2818 (78.8)	2411 (43.8)	4113 (68.0)	2827 (77.3)
Mild	2190 (25.8)	2115 (26.1)	1947 (35.3)	1804 (24.0)	554 (15.5)	1945 (32.3)	1384 (22.9)	628 (17.1)
Moderate or severe	1072 (12.6)	974 (12.0)	1224 (22.2)	650 (8.7)	172 (4.8)	1138 (20.7)	544 (9.0)	198 (5.4)
Prior use of hormone therapy								
Never	6277 (73.8)	6020 (74.3)	3937 (71.3)	5683 (75.7)	2677 (74.9)	3803 (69.2)	4558 (75.5)	2516 (68.9)
Past	1671 (19.6)	1588 (19.6)	1033 (18.7)	1418 (18.9)	808 (22.6)	1109 (20.2)	1126 (18.6)	1024 (28.0)
Current	554 (6.5)	491 (6.1)	552 (10.0)	403 (5.4)	90 (2.5)	581 (10.6)	354 (5.9)	110 (3.0)
Duration of prior hormone therapy use, y								
<5	1539 (18.1)	1470 (18.1)	1200 (21.7)	1239 (16.5)	570 (15.9)	1363 (24.8)	917 (15.2)	729 (20.0)
5-9	427 (5.0)	356 (4.4)	302 (5.5)	328 (4.4)	153 (4.3)	322 (5.9)	282 (4.7)	179 (4.9)
≥10	263 (3.1)	255 (3.1)	83 (1.5)	259 (3.4)	176 (4.9)	5 (0.1)	284 (4.7)	229 (6.3)

*The numbers may not add up to the total because of missing data.

Table 3. Overall Cardiovascular and Global Index Events

	No. of Cases (Annualized %)*			
	Hormone Therapy (n = 13 816)	Placebo (n = 13 531)	HR (95% CI)†	Estimated Absolute Excess Risk per 10 000 Person-Years (95% CI)‡
	Combined Trials			
CHD§	396 (0.46)	379 (0.44)	1.07 (0.92 to 1.23)	3.1 (–2.6 to 9.4)
Stroke	327 (0.38)	239 (0.29)	1.32 (1.12 to 1.56)	9.3 (3.4 to 15.1)
Total mortality	546 (0.63)	528 (0.63)	1.02 (0.90 to 1.15)	1.2 (–6.0 to 8.6)
Global index‖	1601 (1.94)	1467 (1.81)	1.08 (1.00 to 1.16)	14.5 (1.7 to 28.2)
	CEE Trial			
	CEE (n = 5310)	Placebo (n = 5429)		
CHD§	201 (0.54)	217 (0.57)	0.95 (0.78 to 1.16)	–2.9 (–13.2 to 8.3)
Stroke	168 (0.45)	127 (0.33)	1.33 (1.05 to 1.68)	10.9 (1.6 to 20.3)
Total mortality	297 (0.79)	292 (0.75)	1.04 (0.88 to 1.22)	3.2 (–8.9 to 16.0)
Global index‖	747 (2.06)	744 (2.01)	1.02 (0.92 to 1.13)	4.0 (–13.0 to 26.1)
	CEE + MPA Trial			
	CEE+MPA (n = 8506)	Placebo (n = 8102)		
CHD§	195 (0.41)	153 (0.34)	1.23 (0.99 to 1.53)	7.8 (–0.3 to 16.0)
Stroke	159 (0.33)	112 (0.25)	1.31 (1.03 to 1.68)	7.8 (0.8 to 14.2)
Total mortality	249 (0.52)	236 (0.52)	1.00 (0.83 to 1.19)	0 (–9.6 to 10.0)
Global index‖	854 (1.84)	723 (1.65)	1.13 (1.02 to 1.25)	21.5 (4.3 to 39.6)

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate.
*Annualized percentage defined as cases per 100 person-years.
†Cox regression model stratified according to age (50-54, 55-59, 60-69, 70-79 years), prior cardiovascular disease, and randomization status in the Dietary Modification Trial.
‡Calculated as [annualized percentage in placebo group × (HR in placebo group – 1)] × 1000. The 95% CIs were estimated by bootstrap methods (however, bootstrap methods may introduce some inaccuracies).
§Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
‖Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

(P=.03). The pattern of increasing absolute excess risks across age categories was observed in both trials. In the CEE trial, the higher absolute excess risks of death and global index events in the oldest age group appeared to differ from the reduced risks at ages 50 to 59 years (P=.02 and P=.01, respectively).

In women with less than 10 years since menopause, there were no apparent effects of hormone therapy on absolute excess risks of CHD, total mortality, or global index in the combined trials (FIGURE 2). However, there were excess risks of stroke in each category for years since menopause, and the 95% CI excluded 1 for the category of women with less than 10 years since menopause. Increasing absolute excess risks were observed for CHD, total mortality, and global index events in women more distant from menopause but only the 17 additional CHD events in women with 20 or more years since menopause approached statistical significance compared with the reduction of 6 events in women with less than 10 years since menopause (P=.03). The patterns across menopause categories were consistent across the 2 trials.

Additional Analyses

There was a high correlation between age and years since menopause (r=0.71). The nonsignificant modification of age relative to the effect of hormone therapy on CHD in the combined trials (P for trend=.16) became even weaker with additional adjustment on years since menopause (P for trend=.83). The relationship of years since menopause to the HR for CHD also was attenuated (from P=.02 to P=.07) with additional adjustment for age.

There were no significant trends for hormone therapy by years since last exposure to hormones (endogenous or exogenous) and no significant interactions of prior hormone use or oophorectomy status with in-trial hormone effects by age or by years since menopause. However, vasomotor symptoms at baseline may have influenced the results for CHD by both age and years since menopause. The possible 3-way interactions of vasomotor symptoms with hormone therapy effects on the HR trend by age (P=.04) and by years since menopause (P=.06) appeared to be due to trends across these categories in the 12% to 17% of women in the trials with moderate or severe vasomotor symptoms (P for trend <.01; TABLE 6 and TABLE 7). There were not any similar trends in the women with no or mild vasomotor symptoms at baseline (data not shown). There were no apparent effects of hormone therapy on CHD in women with vasomotor symptoms aged 50 to 59 years or in women with less than 10 years since menopause. Increased risks for CHD, stroke, and global index events were seen in women aged 70 to 79 years at baseline and for CHD and global index events in women with 20 or more years since menopause. The findings were similar for women taking CEE and CEE + MPA (data not shown).

The vasomotor symptoms in the older women appeared to be related to hormonal factors to a similar extent as those in younger women because a large majority reported their first symptoms starting at menopause. The vasomotor symptoms responded to hormone therapy in the trial to a similar extent, with the exception of a lesser response of night sweats to CEE + MPA in women aged 70 to 79 years or with 20 or more years since menopause (data not shown). Risk factors for CHD tended to be more adverse in the women with vasomotor symptoms in each age group and in each category for years since menopause. However, the results did not change when the analyses for interaction were repeated with adjustment for risk factors. Similarly, adjustment for adherence to study pills did not change the results.

Sensitivity analyses that censored the data when a woman became nonadherent generally increased the HRs for outcomes but did not show any substan-

tial modification of hormone effects by age or years since menopause. Other models suggested a time-dependent effect of hormone therapy in the combined trials for CHD (but not stroke), with higher risks in the first 2 years and decreasing risk thereafter ($P=.01$). Even though power was limited by small numbers of events, the direction of time-dependent effects were similar within categories of age or years since menopause, and there were no interactions of time-dependent effects on HRs across the age or years since menopause categories.

COMMENT

Although not statistically significant, these secondary analyses suggest that the effect of hormones on CHD may be modified by years since menopause and by the presence of vasomotor symptoms, with the highest risks in women who were 20 or more years since menopause (or aged ≥70 years). Coronary heart disease tended to be nonsignificantly reduced by hormone therapy in younger women or women with less than 10 years since menopause, and the risk of total mortality was reduced in women aged 50 to 59 years. We did not have adequate statistical power to assess outcomes in the women aged 50 to 54 years or less than 5 years since menopause. As previously reported, CEE appeared to be associated with lower risk of CHD than CEE + MPA.[4] Importantly, the risk of stroke was not influenced by years since menopause, the presence of vasomotor symptoms, or drug regimen, although there was no increased risk of stroke in women aged 50 to 59 years.

Our findings are consistent with findings from observational studies of the association of years since menopause

Table 4. Cardiovascular and Global Index Events by Age at Baseline

	Age Group at Randomization									
	50-59 y			60-69 y			70-79 y			
	No. of Cases			No. of Cases			No. of Cases			
	Hormone Therapy (n = 4476)	Placebo (n = 4356)	HR (95% CI)*	Hormone Therapy (n = 6240)	Placebo (n = 6122)	HR (95% CI)*	Hormone Therapy (n = 3100)	Placebo (n = 3053)	HR (95% CI)*	*P* Value for Trend†
Combined Trials										
CHD‡	59	61	0.93 (0.65-1.33)	174	178	0.98 (0.79-1.21)	163	131	1.26 (1.00-1.59)	.16
Stroke	44	37	1.13 (0.73-1.76)	156	102	1.50 (1.17-1.92)	127	100	1.21 (0.93-1.58)	.97
Total mortality	69	95	0.70 (0.51-0.96)	240	225	1.05 (0.87-1.26)	237	208	1.14 (0.94-1.37)	.06
Global index§	278	278	0.96 (0.81-1.14)	717	661	1.08 (0.97-1.20)	606	528	1.14 (1.02-1.29)	.09
CEE Trial										
	CEE (n = 1637)	Placebo (n = 1673)		CEE (n = 2387)	Placebo (n = 2465)		CEE (n = 1286)	Placebo (n = 1291)		
CHD‡	21	34	0.63 (0.36-1.09)	96	106	0.94 (0.71-1.24)	84	77	1.13 (0.82-1.54)	.12
Stroke	18	21	0.89 (0.47-1.69)	84	54	1.62 (1.15-2.27)	66	52	1.21 (0.84-1.75)	.62
Total mortality	34	48	0.71 (0.46-1.11)	129	131	1.02 (0.80-1.30)	134	113	1.20 (0.93-1.55)	.18
Global index§	114	140	0.82 (0.64-1.05)	333	342	1.01 (0.86-1.17)	300	262	1.16 (0.98-1.37)	.01
CEE + MPA Trial										
	CEE+MPA (n = 2839)	Placebo (n = 2683)		CEE+MPA (n = 3853)	Placebo (n = 3657)		CEE+MPA (n = 1814)	Placebo (n = 1762)		
CHD‡	38	27	1.29 (0.79-2.12)	78	72	1.03 (0.74-1.43)	79	54	1.48 (1.04-2.11)	.70
Stroke	26	16	1.41 (0.75-2.65)	72	48	1.37 (0.95-1.97)	61	48	1.21 (0.82-1.78)	.56
Total mortality	35	47	0.69 (0.44-1.07)	111	94	1.09 (0.83-1.44)	103	95	1.06 (0.80-1.41)	.19
Global index§	164	138	1.10 (0.87-1.38)	384	319	1.15 (0.99-1.34)	306	266	1.13 (0.95-1.33)	.96

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate.
*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using age as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for age and the interaction between trials and age.
‡Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
§Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

with carotid intima-media thickness.[14,15] Although age and years since menopause are highly correlated, in our analyses years since menopause appeared to influence hormone effects on CHD somewhat more than chronological age. Estrogen may have dual and opposing actions, retarding the earlier stages of atherosclerosis through beneficial effects on endothelial function and blood lipids, but triggering acute events in the presence of advanced lesions through procoagulant and inflammatory mechanisms.[5,6] Our findings are consistent with a neutral effect of hormone therapy in women soon after menopause (who are likely to have fewer complicated lesions), but progressively more unfavorable effects on CHD risk in later years. The trends across categories of age and years since menopause appeared to be somewhat stronger in women without a history of prior cardiovascular disease (although this trend was not significantly different from women with prior cardiovascular disease, possibly due to small numbers). It is not known why the effects of hormone therapy on stroke overall, and in women close to menopause, differ from the effects of therapy on CHD. Risk of stroke on hormone therapy was elevated by 77% in women with 10 or less years since menopause but by a nonsignificant 13% in women aged 50 to 59 years. The risk for stroke in women with less than 10 years since menopause attenuated to a nonsignificant increase of 23% when those with prior cardiovascular disease and who were older than 60 years were excluded.

This analysis of the WHI data provides some convergence with information from observational studies, ani-

Table 5. Cardiovascular and Global Index Events by Years Since Menopause at Baseline

	Years Since Menopause									
	<10			10-19			≥20			
	No. of Cases			No. of Cases			No. of Cases			
	Hormone Therapy (n = 3608)	Placebo (n = 3529)	HR (95% CI)*	Hormone Therapy (n = 4483)	Placebo (n = 4494)	HR (95% CI)*	Hormone Therapy (n = 4081)	Placebo (n = 4122)	HR (95% CI)*	*P* Value for Trend†
Combined Trials										
CHD‡	39	51	0.76 (0.50-1.16)	113	103	1.10 (0.84-1.45)	194	158	1.28 (1.03-1.58)	.02
Stroke	41	23	1.77 (1.05-2.98)	100	79	1.23 (0.92-1.66)	142	113	1.26 (0.98-1.62)	.36
Total mortality	53	67	0.76 (0.53-1.09)	142	149	0.98 (0.78-1.24)	267	240	1.14 (0.96-1.36)	.51
Global index§	222	203	1.05 (0.86-1.27)	482	440	1.12 (0.98-1.27)	675	632	1.09 (0.98-1.22)	.82
CEE Trial										
	CEE (n = 826)	Placebo (n = 817)		CEE (n = 1436)	Placebo (n = 1500)		CEE (n = 2231)	Placebo (n = 2319)		
CHD‡	8	16	0.48 (0.20-1.17)	47	50	0.96 (0.64-1.44)	117	111	1.12 (0.86-1.46)	.15
Stroke	17	8	2.24 (0.92-5.44)	43	30	1.47 (0.92-2.35)	86	72	1.20 (0.87-1.65)	.24
Total mortality	14	21	0.65 (0.33-1.29)	63	70	0.93 (0.66-1.30)	169	152	1.16 (0.93-1.45)	.42
Global index§	60	62	0.94 (0.65-1.36)	179	177	1.05 (0.85-1.29)	391	381	1.07 (0.92-1.23)	.63
CEE + MPA Trial										
	CEE+MPA (n = 2782)	Placebo (n = 2712)		CEE+MPA (n = 3047)	Placebo (n = 2994)		CEE+MPA (n = 1850)	Placebo (n = 1803)		
CHD‡	31	35	0.88 (0.54-1.43)	66	53	1.23 (0.85-1.77)	77	47	1.66 (1.14-2.41)	.05
Stroke	24	15	1.58 (0.81-3.05)	57	49	1.12 (0.76-1.64)	56	41	1.35 (0.89-2.03)	.87
Total mortality	39	46	0.81 (0.52-1.24)	79	79	1.03 (0.75-1.41)	98	88	1.11 (0.83-1.49)	.93
Global index§	162	141	1.09 (0.87-1.37)	303	263	1.17 (0.99-1.38)	284	251	1.13 (0.95-1.35)	.92

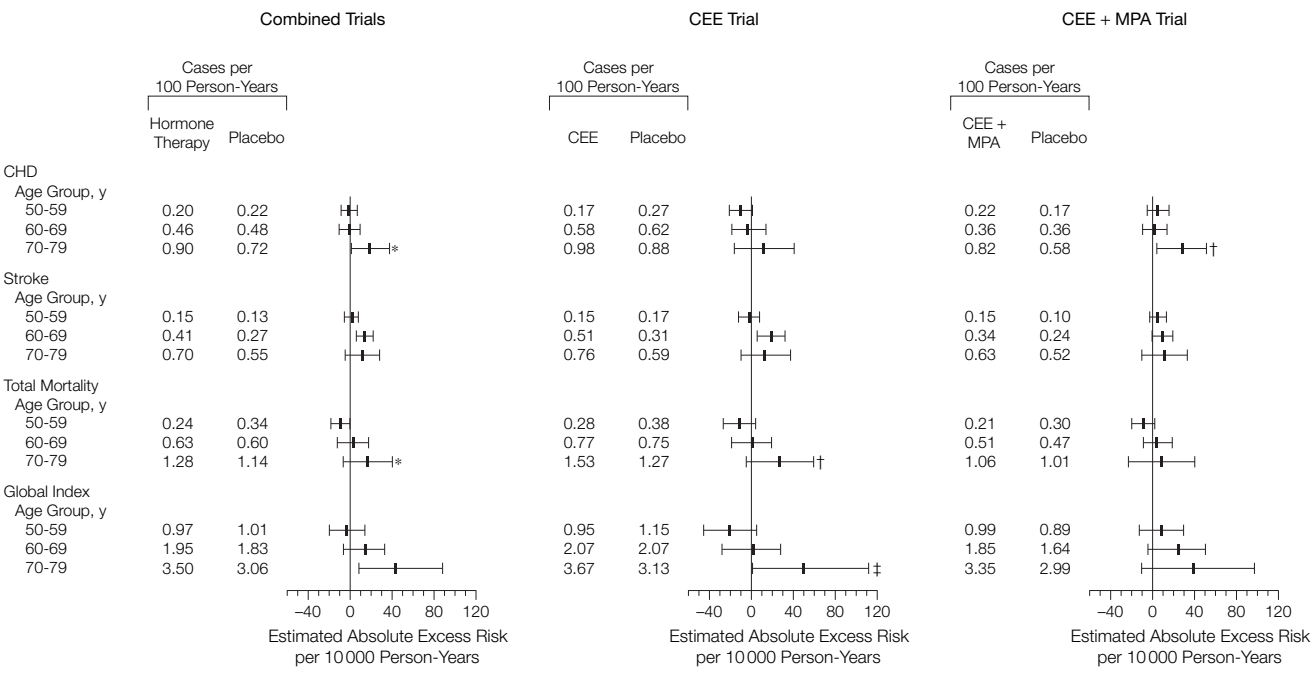
Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate.
*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using age as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for years since menopause and the interaction between trials and years since menopause.
‡Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
§Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

mal studies, and laboratory studies, which have focused mainly on the effects of estrogen on normal coronary arteries or women without clinical cardiovascular disease.[5,6,16] However, differences remain. One observational study examining this issue predicted a reduced risk of CHD in healthy women who commenced hormone therapy within 4 years since menopause, and no effect in women with 10 or more years since menopause,[7] while our combined trial data find a nonsignificant reduction in women starting hormone therapy during 10 or less years since menopause and increasing risks thereafter. Women's Health Initiative data suggest an advantage for CEE compared with CEE + MPA in regard to CHD, but the observational data would predict similar effects for these formulations (at least for CEE with the cyclical MPA more commonly used in observational studies).[1,7,16]

There is also a divergence in regard to secondary prevention, with observational study but not trial data on women with existing disease suggesting CHD benefit for hormone users.[1,2,17,18] The inclusion of a small proportion of women with prior disease in this analysis of trial data and in similar analyses of observational study data did not change the estimates of CHD risk on hormone therapy by age or years since menopause appreciably, possibly because there were relatively few such women in younger age categories, and in the older age categories the presence of prior CHD is but one of many other factors contributing to risk.[7] Some observational and trial data agree in predicting early harm in women after initiation of hormone therapy.[2,3,17-20] Confounding due to the healthier characteristics of hormone users, and failure to account for years since hormone therapy initiation, would lead to overestimation of benefit for CHD in observational studies, even after adjusting for measurable factors.[5]

Absolute risks may be more helpful than HRs to clinicians weighing the pros and cons of hormone therapy for particular patients. Because of low event rates in more recently menopausal women, the absolute excess risk will be very small, even in the presence of some increased relative risk due to hormone therapy. On the other hand the higher event rates in women more distant from menopause, together with their increased HRs, translate into large absolute excess risks. The low or absent excess risks of CHD in women with less than 10 years since menopause may be somewhat reassuring to women considering the use of hormones in the first few years after menopause. However, the increased absolute risk of stroke in this subgroup (although not apparent in women aged 50-59 years in the CEE trial and at-

Figure 1. Estimated Absolute Excess Risk per 10 000 Person-Years by Age Group at Baseline



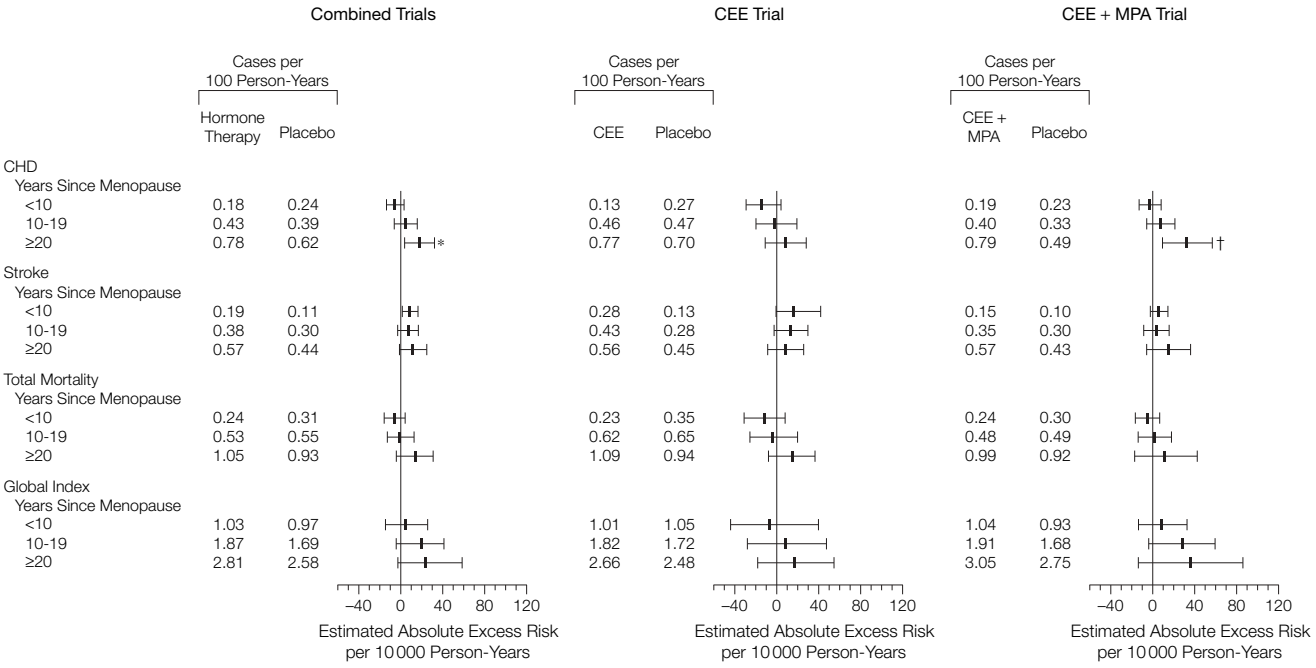
The estimated absolute excess risk may differ slightly from the absolute excess risk derived from the differences in cases per 100 person-years between active hormone and placebo groups. Estimated absolute excess risk was per 10 000 person-years calculated as [annualized percentage in the placebo group × (hazard ratio in the placebo group − 1)] × 1000. Error bars indicate 95% confidence intervals, estimated using bootstrap methods. CEE indicates conjugated equine estrogens; CHD, coronary heart disease; MPA, medroxyprogesterone acetate.

*P = .03 compared with the age group of 50 to 59 years.
†P = .02 compared with the age group of 50 to 59 years.
‡P = .01 compared with the age group of 50 to 59 years.

tenuated after excluding women older than 60 years in the years since menopause analyses) implies that, at a minimum, screening and treatment of risk factors for stroke would be advisable before considering hormone therapy.

For CEE + MPA, the risk of breast cancer also needs to be considered. In women with less than 10 years since

Figure 2. Estimated Absolute Excess Risk per 10 000 Person-Years by Years Since Menopause at Baseline



The estimated absolute excess risk may differ slightly from the absolute excess risk derived from the differences in cases per 100 person-years between active hormone and placebo groups. Estimated absolute excess risk per 10 000 person-years calculated as [annualized percentage in the placebo group × (hazard ratio in the placebo group − 1)] × 1000. Error bars indicate 95% confidence intervals, estimated using bootstrap methods. CEE indicates conjugated equine estrogens; CHD, coronary heart disease; MPA, medroxyprogesterone acetate.
*P = .03 compared with the less than 10 years since menopause group.
†P = .04 compared with the less than 10 years since menopause group.

Table 6. Cardiovascular and Global Index Events in Subgroup of Participants with Moderate or Severe Vasomotor Symptoms at Baseline in the Combined Trials

	Age Group at Randomization										
	50-59 y			60-69 y			70-79 y			*P* Value	
	No. of Cases			No. of Cases			No. of Cases				
	Hormone Therapy (n = 1097)	Placebo (n = 1030)	HR (95% CI)*	Hormone Therapy (n = 691)	Placebo (n = 665)	HR (95% CI)*	Hormone Therapy (n = 197)	Placebo (n = 196)	HR (95% CI)*	Trend†	Interaction With Vasomotor Symptoms‡
CHD§	17	19	0.86 (0.44-1.65)	31	25	1.20 (0.70-2.04)	27	6	5.08 (2.08-12.40)	<.01	.04
Stroke	14	11	1.09 (0.49-2.43)	16	20	0.75 (0.39-1.45)	12	3	3.94 (1.09-14.23)	.28	.34
Total mortality	20	22	0.85 (0.46-1.56)	35	27	1.27 (0.77-2.12)	24	15	1.56 (0.81-3.00)	.22	.72
Global index‖	69	66	0.98 (0.70-1.38)	88	85	1.02 (0.75-1.37)	62	32	2.10 (1.35-3.27)	.02	.15

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.
*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using age as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for age and the interaction between trials and age.
‡Likelihood ratio test for 3-way interaction among hormone therapy, age, and vasomotor symptoms (none vs mild vs moderate or severe).
§Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
‖Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

menopause, there were 72 (0.32%) cases of breast cancer while taking CEE + MPA compared with 57 (0.28%) cases while taking placebo (HR, 1.19; 95% CI, 0.84-1.70). By contrast, the increasing absolute risks of CHD in older women or women more distant from menopause (most marked in women aged >70 years or ≥20 years past menopause), together with their increased risks of stroke, breast cancer, and venous thromboembolism, would in general contraindicate the use of hormones for disease prevention in these groups.

The findings for vasomotor symptoms are intriguing and of potential importance to clinicians but need confirmation. The higher risks in women more distant from menopause appeared to be concentrated in the small subset of women with moderate or severe vasomotor symptoms. It is possible that vasomotor symptoms in recently menopausal women represent the reaction of vessels with normal endothelial function to estrogen withdrawal but persistent symptoms may signify something different in older women. If confirmed elsewhere (eg, by reanalyses of existing observational studies and clinical trials), the clinical implication might be that while treatment of vasomotor symptoms with hormone therapy in younger women remains an option, the reverse might apply to older women. Rather, the presence of moderate or severe vasomotor symptoms at older ages might signal the need for identification and treatment of risk factors for CHD. Although CHD risk factors were more frequent in women with vasomotor symptoms, analyses adjusting for these factors did not change the trend statistic, suggesting that hormone therapy interactions with other unmeasured risk factors in women with vasomotor symptoms may underlie the increasing risk in women more distant from menopause.

The current analyses are most pertinent to the effects of initiation of exogenous hormone use but also provide some limited information regarding the potential effects of prolonged use, taking into account indicators of hormone status at trial enrollment. Within the relatively short trial durations, CHD risk related to hormone therapy appeared to decrease over time. However, the significance of this trend over time depends on both the initial increase in risk, as well as the subsequent decrease, and hence may partially represent a survivor effect. In addition, the decreasing risk is confounded by diminishing compliance over time. Current or past hormone users and never users appeared to have similar trends toward increasing risks by years since menopause during the trial, providing indirect evidence that longer duration of use is not protective. It is not feasible to test hormone effects over very long periods of use in clinical trials, and observational studies have yielded conflicting results.[16,20] Unlike statin drugs, which have beneficial effects for both atherosclerosis and clinical events irrespective of the underlying state of the arteries,[21,22] hormone therapy has a putative beneficial effect on early atherosclerosis,[5,6] no effect on advanced atherosclerosis,[23,24] and an early increase in risk of CHD events when advanced atherosclerosis may be present.[2,3,25] Because age-related progression of atherosclerosis is likely to continue even in the face of hormone therapy, use over decades could potentially result in an eventual increase in CHD events. Hence, even if ongoing imaging trials confirm a slowing of early atherosclerosis,[26,27] it would be unwise to extrapolate such findings to clinical benefit with continued use into old age.

These analyses are based on systematically ascertained outcomes in a set-

Table 7. Cardiovascular and Global Index Events in Subgroup of Participants With Moderate or Severe Vasomotor Symptoms at Baseline in the Combined Trials

	Years Since Menopause										
	<10			10-19			≥20				
	No. of Cases			No. of Cases			No. of Cases			*P* Value	
	Hormone Therapy (n = 833)	Placebo (n = 757)	HR (95% CI)*	Hormone Therapy (n = 557)	Placebo (n = 555)	HR (95% CI)*	Hormone Therapy (n = 440)	Placebo (n = 459)	HR (95% CI)*	Trend†	Interaction With Vasomotor Symptoms‡
CHD§	13	17	0.84 (0.40-1.77)	17	13	1.38 (0.63-3.00)	39	16	2.76 (1.53-4.97)	<.01	.06
Stroke	10	3	3.36 (0.92-12.24)	13	11	1.02 (0.44-2.37)	16	16	0.92 (0.44-1.93)	.31	.59
Total mortality	14	16	0.93 (0.44-1.96)	17	15	1.21 (0.58-2.51)	42	29	1.60 (0.99-2.60)	.14	.41
Global index‖	55	47	1.15 (0.77-1.71)	59	47	1.23 (0.82-1.84)	85	72	1.30 (0.94-1.80)	.30	.48

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.
*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using years since menopause as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for years since menopause and the interaction between trials and years since menopause.
‡Likelihood ratio test for 3-way interaction among hormone therapy, years since menopause, and vasomotor symptoms (none vs mild vs moderate or severe).
§Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
‖Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

ting of randomized controlled trials, thus avoiding some of the potential biases of observational studies. The conclusions relating to harm in women more distant from menopause are more robust because of the larger numbers of clinical events. The conclusions based on the analyses of women closer to menopause are less robust due to smaller numbers, as are the analyses involving vasomotor symptoms. Time of menopause may not be accurately ascertained in women who have undergone a hysterectomy. Nonadherence may have affected the results. At the end of the trials, 54% of participants were no longer taking CEE and 42% were no longer taking CEE + MPA. The results are derived from relatively short durations of treatment but the average of 4 to 5 years of receiving treatment in the trials is longer than most women would need for treatment of vasomotor symptoms. Multiple statistical tests were performed, raising a distinct possibility that several of the positive findings occurred by chance. The possibility of type I error is increased by the fact that these analyses were partly stimulated by the initial findings from the trials. The results are dependent on the analytic approach used, which differs in this compared with previous publications from the WHI trials. In previous WHI studies using continuous variables, the significance of the interaction of years since hysterectomy on CHD in the trial of CEE was $P=.06$ compared with $P=.15$ for years since menopause in the current analysis using coded variables.[3] In the trial of CEE + MPA, the significance for years since menopause changed from $P=.33$ to $P=.05$.[4] Only one form of oral estrogen and one form of oral progestin taken daily were included in the trials, and it may be that different results would have been obtained if other regimens (eg, transdermal estradiol, progesterone, or cyclic therapy) were tested.

These analyses, although not definitive, suggest that the health consequences of hormone therapy may vary by distance from menopause, with no apparent increase in CHD risk for women close to menopause, and particularly high risks in women who are distant from menopause and have vasomotor symptoms. We did not identify any subgroup with reduced risk of CHD, although total mortality was reduced among women aged 50 to 59 years. The findings regarding potential modifying effects of vasomotor symptoms warrant further study. The absence of excess absolute risk of CHD and the suggestion of reduced total mortality in younger women offers some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms, but does not necessarily imply an absence of harm over prolonged periods of hormone use. In contrast, risk of stroke did not depend on years since menopause or the presence of vasomotor symptoms. The findings are consistent with current recommendations that hormone therapy be used in the short-term for relief of moderate or severe vasomotor symptoms, but not in the longer term for prevention of cardiovascular disease.[28,29]

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Author Contributions: Dr Rossouw had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Prentice, Manson, Barad, Ko, LaCroix, Stefanick.
Analysis and interpretation of data: Rossouw, Prentice, Manson, Wu, Barad, Barnabei, LaCroix, Margolis.
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Phosphodiesterase Type-5 Inhibitors and the Reemerging HIV Epidemic

To the Editor: The Commentary by Dr Jaffe and colleagues[1] addressed the reemerging human immunodeficiency virus (HIV) epidemic among men who have sex with men in the United States. The authors describe substance abuse, particularly methamphetamines and alcohol, as one of the factors that contribute to unsafe sexual behaviors. Important substances of abuse that were not mentioned in the Commentary are phosphodiesterase type-5 inhibitors: sildenafil, vardenafil, and tadalafil. Phosphodiesterase type-5 inhibitors are indicated for the treatment of impotence but can enhance erectile function in the absence of clinical impotence and are often used in combination with other recreational drugs.[2]

In multiple surveys of US men who have sex with men, current or recent sildenafil use (with and without concomitant illicit drug use) was reported by 6% to 31% of respondents and was associated with increased rates of high-risk behaviors (eg, unprotected anal intercourse, HIV serodiscordant partners, and methamphetamine use) and diagnosis of sexually transmitted infections, including early syphilis and HIV.[3] More recent data have corroborated those findings.[4] Discussion of phosphodiesterase type-5 inhibitor abuse in the context of the US HIV epidemic is warranted because at the point of prescribing a phosphodiesterase type-5 inhibitor, clinicians can initiate risk reduction interventions, including sexually transmitted infection and HIV screening.[5] In addition, we believe that federal agencies should carefully monitor the use and marketing of phosphodiesterase type-5 inhibitors and work together to limit the effects of these drugs on the reemerging HIV epidemic and other sexually transmitted infections.[5]

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This letter was shown to Dr Jaffe, who declined to reply on behalf of the authors. —ED.

CORRECTION

Incorrect Number: In the Original Contribution entitled "Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause" published in the April 4, 2007, issue of *JAMA* (2007;297[13]:1465-1477), a number was incorrectly reported in the abstract and in Table 3. On page 1465, the first sentence in the Results section of the abstract should be "In the combined trials, there were 396 cases of CHD and 327 cases of stroke in the hormone therapy group vs 370 cases of CHD and 239 cases of stroke in the placebo group." In Table 3, first line of the table, "CHD§," in second column under "Placebo," the values should be changed from "379 (0.44)" to "370 (0.44)."