

Conjugated Equine Estrogens and Coronary Heart Disease

The Women's Health Initiative

Judith Hsia, MD; Robert D. Langer, MD, MPH; JoAnn E. Manson, MD, DrPH; Lewis Kuller, MD, DrPH; Karen C. Johnson, MD, MPH; Susan L. Hendrix, DO; Mary Pettinger, MS; Susan R. Heckbert, MD, PhD; Nancy Greep, MD; Sybil Crawford, PhD; Charles B. Eaton, MD; John B. Kostis, MD; Pat Caralis, MD; Ross Prentice, PhD; for the Women's Health Initiative Investigators

Background: In recent randomized trials, conjugated equine estrogens (CEE) with continuous medroxyprogesterone acetate provided no protection against coronary heart disease in postmenopausal women and may have increased cardiac risk. These trials did not address the role of unopposed estrogen for coronary protection.

Methods: A total of 10 739 women aged 50 to 79 years at baseline (mean age, 63.6 years) who had previously undergone hysterectomy were randomized to receive CEE, 0.625 mg/d, or placebo at 40 US clinical centers beginning in 1993. The trial was terminated early after 6.8 years of follow-up (planned duration, 8.5 years). This report includes final, centrally adjudicated results for the primary efficacy outcome (myocardial infarction or coronary death), secondary coronary outcomes, and subgroup analyses.

Results: During the active intervention period, 201 coronary events were confirmed among women assigned to receive CEE compared with 217 events among women

assigned to receive placebo (hazard ratio, 0.95; nominal 95% confidence interval, 0.79-1.16). Among women aged 50 to 59 years at baseline, the hazard ratio for the primary outcome was 0.63 (nominal 95% confidence interval, 0.36-1.08). In that age group, coronary revascularization was less frequent among women assigned to receive CEE (hazard ratio, 0.55; nominal 95% confidence interval, 0.35-0.86), as were several composite outcomes, which included the primary outcome and coronary revascularization (hazard ratio, 0.66; nominal 95% confidence interval, 0.44-0.97).

Conclusions: Conjugated equine estrogens provided no overall protection against myocardial infarction or coronary death in generally healthy postmenopausal women during a 7-year period of use. There was a suggestion of lower coronary heart disease risk with CEE among women 50 to 59 years of age at baseline.

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THE WOMEN'S HEALTH INITIATIVE includes 2 randomized, placebo-controlled hormone trials, the estrogen plus progestin trial in women with intact uteri and the estrogen-alone trial in women who had undergone prior hysterectomy.¹ These trials, which were designed to be analyzed separately, both tested the hypothesis that postmenopausal hormone therapy prevents coronary heart disease (CHD) and assessed the overall balance of risks and benefits. In the estrogen plus progestin trial, conjugated equine estrogens (CEE) with daily medroxyprogesterone acetate appeared to augment coronary risk.^{2,3}

The estrogen-alone trial was stopped in March 2003, earlier than planned; preliminary results were reported shortly thereafter.⁴ This analysis reports final results for the primary efficacy outcome of the estrogen-alone trial, which random-

ized 10 739 postmenopausal women who had undergone prior hysterectomy to receive CEE or placebo. In addition to our primary outcome, nonfatal myocardial infarction or coronary death, this analysis includes secondary coronary outcomes, provides detailed analyses of subgroups to further elucidate the primary findings, and explores the relationship between the results of this trial and the previously reported companion trial of CEE with medroxyprogesterone acetate.

METHODS

Details of the study design^{1,4,5} and baseline characteristics⁶ have previously been published. Eligible patients were postmenopausal women 50 to 79 years of age who had undergone prior hysterectomy. Study participants provided informed consent in a document approved by local institutional review boards and were randomly assigned to receive CEE, 0.625 mg/d (Premarin;

Author Affiliations are listed at the end of this article.

Group Information: A complete list of The Women's Health Initiative investigators appears in *JAMA* (2004;291:1701-1712).

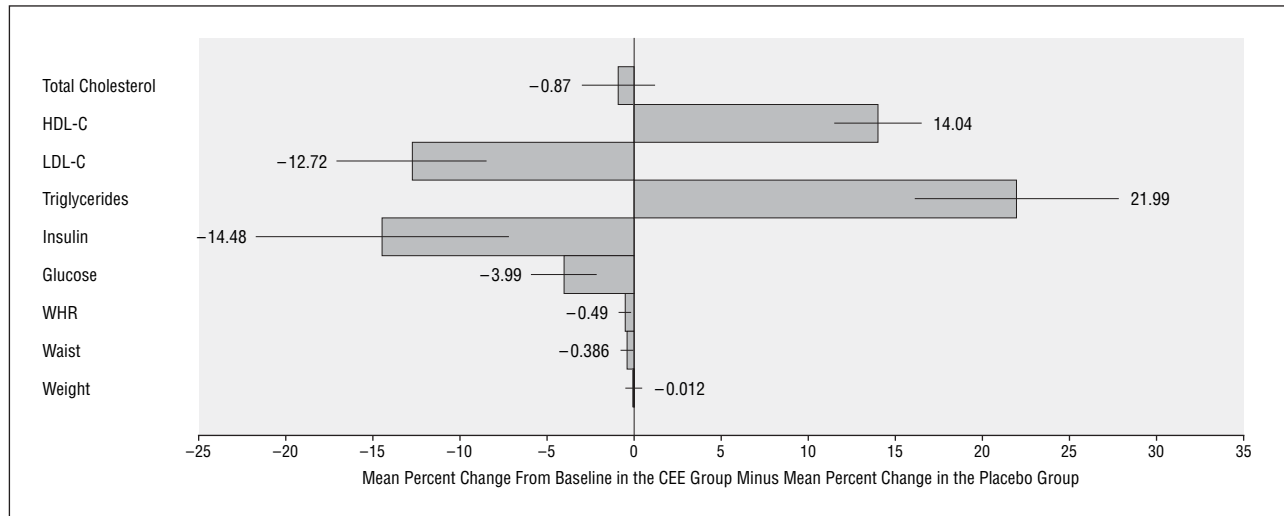


Figure 1. Treatment group differences from baseline to year 1 in several intermediate outcomes. Horizontal lines represent nominal 95% confidence intervals. Physical measures were performed on the entire cohort; laboratory measures were performed in a random 8.6% subsample. Treatment group differences were significant for triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) ($P < .001$ for all), insulin and glucose ($P < .001$), waist-hip ratio (WHR) ($P = .002$), and waist circumference ($P = .02$). CEE indicates conjugated equine estrogens.

Table 1. Coronary Outcomes Among Women Assigned to CEE vs Placebo*

Outcome	No. of Cases (Annualized %)		Hazard Ratio (95% CI)	P Value
	CEE	Placebo		
Primary outcome				
CHD (MI or CHD death)	201 (0.53)	217 (0.56)	0.95 (0.79-1.16)	.63
Nonfatal MI, including silent MI	149 (0.40)	168 (0.43)	0.91 (0.73-1.14)	.43
Nonfatal MI, excluding silent MI	142 (0.38)	161 (0.42)	0.91 (0.73-1.14)	.41
Coronary death	62 (0.16)	63 (0.16)	1.01 (0.71-1.43)	.96
Secondary outcome				
CABG or PCI	253 (0.67)	276 (0.71)	0.93 (0.78-1.10)	.38
Hospitalized angina	265 (0.70)	262 (0.68)	1.02 (0.86-1.21)	.81
Confirmed angina	163 (0.43)	171 (0.44)	0.97 (0.78-1.20)	.77
Hospitalized CHF	185 (0.49)	183 (0.47)	1.03 (0.84-1.26)	.81
Hospitalized CHF with wall motion abnormality	60 (0.16)	69 (0.18)	0.88 (0.62-1.24)	.47
Acute coronary syndrome	395 (1.05)	401 (1.04)	0.99 (0.86-1.14)	.93
MI, CHD death, CABG, and PCI	356 (0.95)	372 (0.96)	0.98 (0.85-1.13)	.78
MI, CHD death, CABG, PCI, and hospitalized angina	466 (1.24)	476 (1.23)	0.99 (0.87-1.13)	.90
MI, CHD death, CABG, PCI, and confirmed angina	380 (1.01)	405 (1.05)	0.95 (0.83-1.09)	.48

Abbreviations: CABG, coronary artery bypass grafting; CEE, conjugated equine estrogens; CHD, coronary heart disease; CHF, congestive heart failure; CI, nominal confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Acute coronary syndrome includes MI and hospitalized angina. Numbers of events do not add up to the totals for categories because some women had more than 1 event.

Wyeth Pharmaceuticals, Madison, NJ), or matching placebo. Blood samples were collected from all participants at baseline and year 1; analyses were performed prospectively on a random 8.6% sample at both time points.⁷ A nested case-control study was also conducted to measure biomarkers in 153 CHD cases (through February 2001) and 365 matched controls at baseline and year 1.

Close-out visits had originally been scheduled to occur between October 2004 and March 2005. The National Institutes of Health decided to stop the trial in February 2004, deeming it unacceptable to subject healthy women in a prevention trial to increased risk of stroke with the possibility that no treatment effect on breast cancer risk would be demonstrated in the remaining intervention period; study participants were informed of this decision on March 1. The initial report of trial

results⁴ was published 6 weeks later, based on outcomes for which adjudication, either local or central, had been completed as of February 29.

During the trial, women reported outcomes by completing a semiannual medical update questionnaire, with roughly 1 of 6 participants completing this questionnaire each month. On or shortly after March 1, 2004, study participants completed an end-of-intervention medical update questionnaire. This article includes all the outcomes in the pipeline on February 29, 2004, but that had not yet made it into the database, as well as outcomes reported on the March 1 questionnaires. Coronary end points were classified by review of medical records; myocardial infarction and coronary death were confirmed by central physician adjudicators and other coronary end points by trained local adjudicators, all blinded to treatment assignment.⁸

CLINICAL OUTCOMES

Classification algorithms included elements of the medical history, cardiac enzymes, and electrocardiograms.^{2,3,8,9} The primary outcome included coronary death,³ clinical myocardial infarction,^{3,8} or silent myocardial infarction determined from serial electrocardiograms, digitally acquired every 3 years and analyzed by a core laboratory.² “Hospitalized angina” required overnight hospitalization with ischemic chest pain or dyspnea; confirmatory testing was not required. “Confirmed angina” was hospitalized angina with a confirmatory stress test and/or more than 70% coronary obstruction by angiography.³

STATISTICAL ANALYSES

Statistical methods have been described previously.²⁻⁴ In brief, hazard ratios with 95% confidence intervals (CIs) were calculated from Cox proportional hazards models stratified by age, prevalent CHD at baseline, and randomization status in the dietary modification trial.¹ Nominal and adjusted CIs are shown for the primary outcome to reflect sequential monitoring of the primary end point. Coronary disease was not a consideration in deciding to stop the trial early.

Subgroup analyses were planned a priori. Logistic regression models for subgroup analyses of biomarker levels were adjusted for age at randomization, year of randomization, and prevalent coronary disease at baseline. Other subgroup analyses used Cox regression stratified by age, prevalent CHD at baseline, and randomization status in the dietary modification trial. Consistency of treatment effects among subgroups was assessed by formal tests of interactions; 26 subgroups were evaluated. The subgroup results should be interpreted with caution, since at least 1 significant finding would be expected by chance based on an .05 nominal level of statistical significance. All reported *P* values are 2-sided. Analyses were performed with SAS statistical software for Windows version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Mean duration of follow-up was 7.1 years; vital status is known for 10 176 participants (94.8%). At the time the trial was stopped, 54.0% of study participants assigned to receive CEE and 53.5% of those assigned to receive placebo had discontinued use of their study medication.⁴

Baseline characteristics have been reported previously⁴ and were balanced between women assigned to receive CEE (*n* = 5310) and those assigned to receive placebo (*n* = 5429). Mean (SD) age was 63.6 years (7.3 years). At baseline, 30.1% reported treated hypertension; 10.3% had untreated hypertension, 7.7% had diabetes mellitus, 15.2% had hypercholesterolemia, and 10.5% were current smokers. Prior myocardial infarction was reported by 3.1% and coronary revascularization by 2.2%.

INTERMEDIATE BIOMARKERS AND RISK FACTORS FOR CHD

Baseline values for blood analytes in the 8.6% biomarker study random sample have been previously reported.⁶ In brief, mean (SD) laboratory values were as follows: total cholesterol, 226.5 mg/dL (41.3 mg/dL) (5.86 mmol/L [1.07 mmol/L]); low-density lipoprotein cholesterol, 137.3 mg/dL (37.8 mg/dL) (3.55 mmol/L [0.78 mmol/L]); high-density lipoprotein cholesterol, 54.2

mg/dL (13.8 mg/dL) (1.40 mmol/L [0.36 mmol/L]); triglycerides, 144.1 mg/dL (67.3 mg/dL) (1.63 mmol/L [0.76 mmol/L]); glucose, 101.9 mg/dL (23.9 mg/dL) (5.66 mmol/L [1.33 mmol/L]); and insulin, 11.0 μ IU/mL (5.5 μ IU/mL) (78.93 pmol/L [39.46 pmol/L]). Compared with placebo recipients, women assigned to receive CEE had greater increases from baseline to year 1 in high-density lipoprotein cholesterol and triglyceride levels and greater reductions in total cholesterol, low-density lipoprotein cholesterol, glucose, and insulin levels (**Figure 1**).

CLINICAL CORONARY OUTCOMES

There were 201 CHD events (nonfatal myocardial infarction or coronary death) among women assigned to CEE and 217 among women assigned to placebo (hazard ratio, 0.95; nominal 95% CI, 0.79-1.16; adjusted CI, 0.76-1.19) (**Table 1**). Of the 317 nonfatal myocardial infarctions, 14 (4.4%) were identified only by serial electrocardiography (7 in the CEE group and 7 in the placebo group), with no associated clinical event. For women adherent to CEE or placebo, defined as taking at least 80% of the prescribed study medication, the hazard ratio was 0.91 (nominal 95% CI, 0.69-1.20).

Among women assigned to CEE, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) were used by 7.4% at baseline, 9.0% at year 1, and 19.8% at year 6. The comparable percentages in the placebo group were 7.9% (*P* = .39 vs CEE), 10.7% (*P* = .004 vs CEE), and 27.3% (*P* < .001 vs CEE). In Cox models that did not include statin use as a time-dependent covariate, the hazard ratio for the primary outcome was 0.95 (Table 1); inclusion of statin use as a time-dependent covariate changed the hazard ratio estimate to 0.97. For the cohort as a whole, no treatment group differences occurred for individual or composite secondary coronary outcomes (Table 1).

TEMPORAL TRENDS

Hazard ratios with nominal 95% CIs for the primary outcome (myocardial infarction or coronary death) at 1-year intervals of follow-up were as follows: year 1, 1.11 (95% CI, 0.64-1.94); year 2, 1.20 (95% CI, 0.69-2.10); year 3, 0.89 (95% CI, 0.50-1.58); year 4, 0.79 (95% CI, 0.45-1.39); year 5, 1.36 (95% CI, 0.80-2.31); and year 6 or later, 0.81 (95% CI, 0.60-1.10). The *z* score for trend, based on Cox proportional hazards modeling with time-dependent treatment effects, was -1.49 (*P* = .14), indicating no significant trend in risk over time.

TRENDS BY AGE

Cumulative hazard rates for the primary outcome are shown by age decade (**Figure 2**) (*P* for interaction = .07). For adherent participants aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline, hazard ratios were 0.61 (nominal 95% CI, 0.25-1.50), 0.86 (95% CI, 0.60-1.25), and 1.10 (95% CI, 0.69-1.73), respectively (*P* for interaction = .35).

Examining the younger age group more closely, among women 50 to 54 years of age at baseline, 8 assigned to receive CEE experienced myocardial infarction or coro-

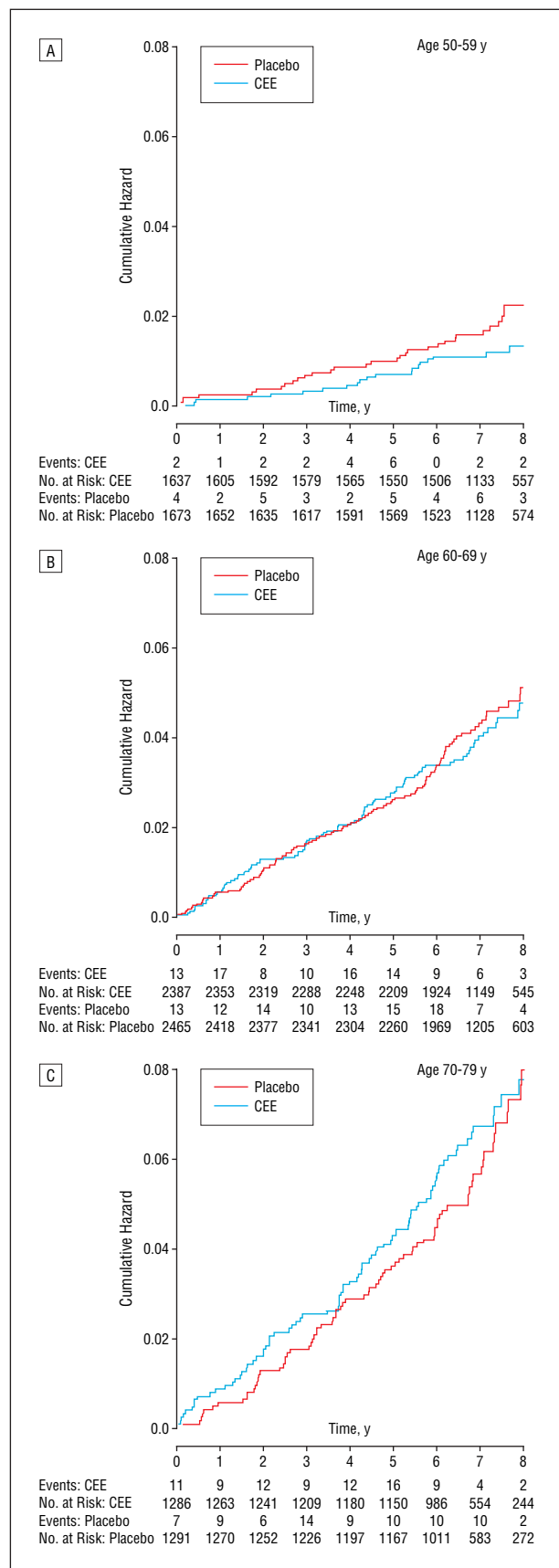


Figure 2. Kaplan-Meier estimates of cumulative hazard ratios for coronary heart disease (myocardial infarction or coronary death) by age decade. A, age 50 to 59 years; B, age 60 to 69 years; and C, age 70 to 79 years. CEE indicates conjugated equine estrogens.

nary death, compared with 14 women assigned to receive placebo (hazard ratio, 0.60; 95% CI, 0.25-1.44). Among women aged 55 to 59 years, 13 assigned to receive CEE and 20 assigned to receive placebo had coronary events (hazard ratio, 0.65; 95% CI, 0.32-1.32).

Secondary coronary outcomes are given by age decade in **Table 2**. Among women aged 50 to 59 years at baseline, coronary revascularization was less frequent among women assigned to receive CEE (hazard ratio, 0.55; 95% CI, 0.35-0.86). Composite outcomes were also less frequent with CEE in this age group. For example, the hazard ratio for myocardial infarction, coronary death, coronary revascularization, and confirmed angina was 0.66 (95% CI, 0.45-0.96). Among women aged 60 to 69 or 70 to 79 years at baseline, secondary coronary outcomes did not differ between treatment groups.

ADDITIONAL SUBGROUP ANALYSES

To determine whether other subgroups of women had lower or higher hazard ratios for coronary events with CEE, we evaluated several demographic and clinical characteristics, baseline levels of lipids, and inflammatory and thrombotic biomarkers (**Table 3**, **Figure 3**, and **Figure 4**). The role of time since menopause in modulating potential risks or benefits for CHD with CEE is shown in Figure 3. Onset of menopause in women who have undergone hysterectomy cannot always be determined with certainty, so proximity to menopause was assessed 4 ways: presence of vasomotor symptoms among women aged 50 to 59 years, time since bilateral oophorectomy, time since hysterectomy, and years since hysterectomy with no postmenopausal hormone therapy. For time since hysterectomy, the hazard ratio with CEE was higher among women who had undergone surgery 20 or more years previously than among the remaining women (*P* for interaction = .06). No such pattern was identified for any of the other variables that assessed proximity to menopause.

The hazard ratio for CHD was similar among white and African American women (Table 3); Hispanic women assigned to receive CEE had a lower estimated hazard ratio of 0.37 (95% CI, 0.12-1.16). Because the number of Hispanic women randomized in the trial was limited and their CHD event rate low, this hazard ratio estimate is unstable. The risk of subsequent coronary events with CEE among women who smoked or had hypertension, diabetes, more coronary risk factors, or prevalent cardiovascular or coronary disease at baseline was similar to that of all women.

The effect of CEE on CHD risk did not differ in subgroups defined by baseline levels of lipoproteins, fibrinogen, or factor VIII:C (Figure 4). In contrast, women with elevated levels of C-reactive protein at baseline appeared at greater risk for CHD with CEE than women with lower levels (*P* for interaction = .04).

COMMENT

Conjugated equine estrogens provided no overall coronary protection in women who had undergone prior hysterectomy, although there was a suggestion of lower CHD risk with CEE in women 50 to 59 years of age. This trial may have been unable to demonstrate a significant

Table 2. Coronary Events With CEE or Placebo by Age at Baseline

Coronary Event	No. of Cases (Annualized %) by Age at Baseline, y									P Value for Interaction
	50-59			60-69			70-79			
	CEE (n = 1637)	Placebo (n = 1673)	HR (95% CI)	CEE (n = 2387)	Placebo (n = 2465)	HR (95% CI)	CEE (n = 1286)	Placebo (n = 1291)	HR (95% CI)	
CHD (MI or coronary death)	21 (0.17)	34 (0.27)	0.63 (0.36-1.08)	96 (0.57)	106 (0.61)	0.94 (0.71-1.24)	84 (0.96)	77 (0.86)	1.11 (0.82-1.52)	.07
CABG or PCI	29 (0.24)	52 (0.42)	0.55 (0.35-0.86)	129 (0.77)	130 (0.75)	0.99 (0.78-1.27)	95 (1.08)	94 (1.06)	1.04 (0.78-1.39)	.09
Hospitalized angina	42 (0.35)	51 (0.41)	0.81 (0.54-1.22)	125 (0.75)	122 (0.71)	1.06 (0.82-1.36)	98 (1.12)	89 (1.00)	1.10 (0.82-1.46)	.37
Confirmed angina*	21 (0.17)	35 (0.28)	0.59 (0.34-1.02)	80 (0.48)	80 (0.46)	1.03 (0.76-1.41)	62 (0.71)	56 (0.63)	1.12 (0.78-1.60)	.18
Acute coronary syndrome†	56 (0.46)	73 (0.59)	0.76 (0.54-1.08)	185 (1.11)	187 (1.08)	1.01 (0.82-1.24)	154 (1.76)	141 (1.58)	1.10 (0.87-1.38)	.18
MI, coronary death, CABG, and PCI	42 (0.35)	65 (0.52)	0.66 (0.44-0.97)	177 (1.06)	177 (1.02)	1.02 (0.83-1.25)	137 (1.56)	130 (1.46)	1.08 (0.85-1.38)	.09
MI, coronary death, CABG, PCI, and hospitalized angina	65 (0.54)	84 (0.68)	0.78 (0.56-1.07)	225 (1.35)	228 (1.32)	1.01 (0.84-1.21)	176 (2.01)	164 (1.84)	1.08 (0.87-1.34)	.13
MI, coronary death, CABG, PCI, and confirmed angina	46 (0.38)	70 (0.56)	0.66 (0.45-0.96)	186 (1.11)	194 (1.12)	0.98 (0.80-1.20)	148 (1.69)	141 (1.58)	1.05 (0.84-1.33)	.11

Abbreviations: CABG, coronary artery bypass grafting; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, nominal confidence interval; HR, nominal hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Confirmed angina requires hospitalization for angina with confirmatory stress test or obstructive coronary disease by angiography.

†Acute coronary syndrome includes myocardial infarction and hospitalized angina.

Table 3. CEE and the Risk of CHD in Various Subgroups*

Subgroup	No. of Cases (Annualized %)		Hazard Ratio (95% CI)	P Value for Interaction
	CEE (n = 5310)	Placebo (n = 5429)		
Race or ethnic group				
White	166 (0.58)	158 (0.54)	1.07 (0.86-1.33)	.13
Non-Hispanic black	28 (0.51)	33 (0.55)	0.92 (0.56-1.53)	
Hispanic	4 (0.18)	11 (0.48)	0.37 (0.12-1.16)	
Level of education				
≤High school or GED	83 (0.67)	88 (0.73)	0.91 (0.67-1.23)	.82
>High school	114 (0.46)	126 (0.48)	0.96 (0.75-1.24)	
Cigarette smoking				
Not current smoker	163 (0.49)	176 (0.51)	0.95 (0.77-1.18)	.83
Current smoker	35 (0.94)	36 (0.91)	0.98 (0.61-1.57)	
Hypertension				
No	63 (0.35)	68 (0.37)	0.96 (0.68-1.35)	>.99
Yes	128 (0.78)	132 (0.79)	0.97 (0.76-1.23)	
Diabetes mellitus				
No	151 (0.44)	166 (0.47)	0.92 (0.74-1.15)	.33
Yes, medication treated	44 (1.61)	47 (1.66)	1.02 (0.67-1.55)	
Yes (all)	50 (1.48)	51 (1.41)	1.13 (0.76-1.69)	
High cholesterol requiring pills				
No	132 (0.47)	131 (0.47)	1.00 (0.78-1.27)	.64
Yes	49 (1.04)	60 (1.16)	0.90 (0.62-1.32)	
Coronary risk factors				
None	25 (0.19)	29 (0.22)	0.86 (0.51-1.47)	.82
1-2	134 (0.72)	139 (0.75)	0.96 (0.76-1.22)	
≥3	19 (2.69)	18 (2.36)	1.13 (0.57-2.21)	
Presence of cardiovascular disease at baseline				
No	150 (0.43)	163 (0.46)	0.95 (0.76-1.19)	.81
Yes	50 (1.96)	50 (1.94)	0.97 (0.65-1.44)	
Presence of CHD at baseline				
No	162 (0.45)	179 (0.49)	0.93 (0.75-1.15)	.33
Yes	38 (2.61)	32 (2.13)	1.12 (0.69-1.80)	

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, nominal confidence interval; GED, general equivalency diploma.

*CHD includes nonfatal myocardial infarction and coronary death. Hazard ratios with nominal 95% CIs are adjusted for age and prevalent CHD at baseline.

P values are for the interaction between the subgroup variable and treatment assignment. Hypertension was defined as treated hypertension or a measured blood pressure of 140/90 mm Hg or higher. Baseline risk factors for CHD included current cigarette smoking, hypertension, self-reported diabetes, and high cholesterol levels. The presence of cardiovascular disease at baseline was defined as prior myocardial infarction, coronary revascularization, stroke, or transient cerebral ischemia. The presence of CHD at baseline was defined as a history of myocardial infarction or coronary revascularization. Because of missing data for some baseline variables, numbers do not always add up to the total number of cases in the treatment group. Data were complete for hypertension, diabetes, myocardial infarction, stroke, and transient cerebral ischemia. Some data were missing for cigarette smoking (1.1%), high cholesterol levels (10.5%), educational level (1.8%), and coronary revascularization (1.5%).

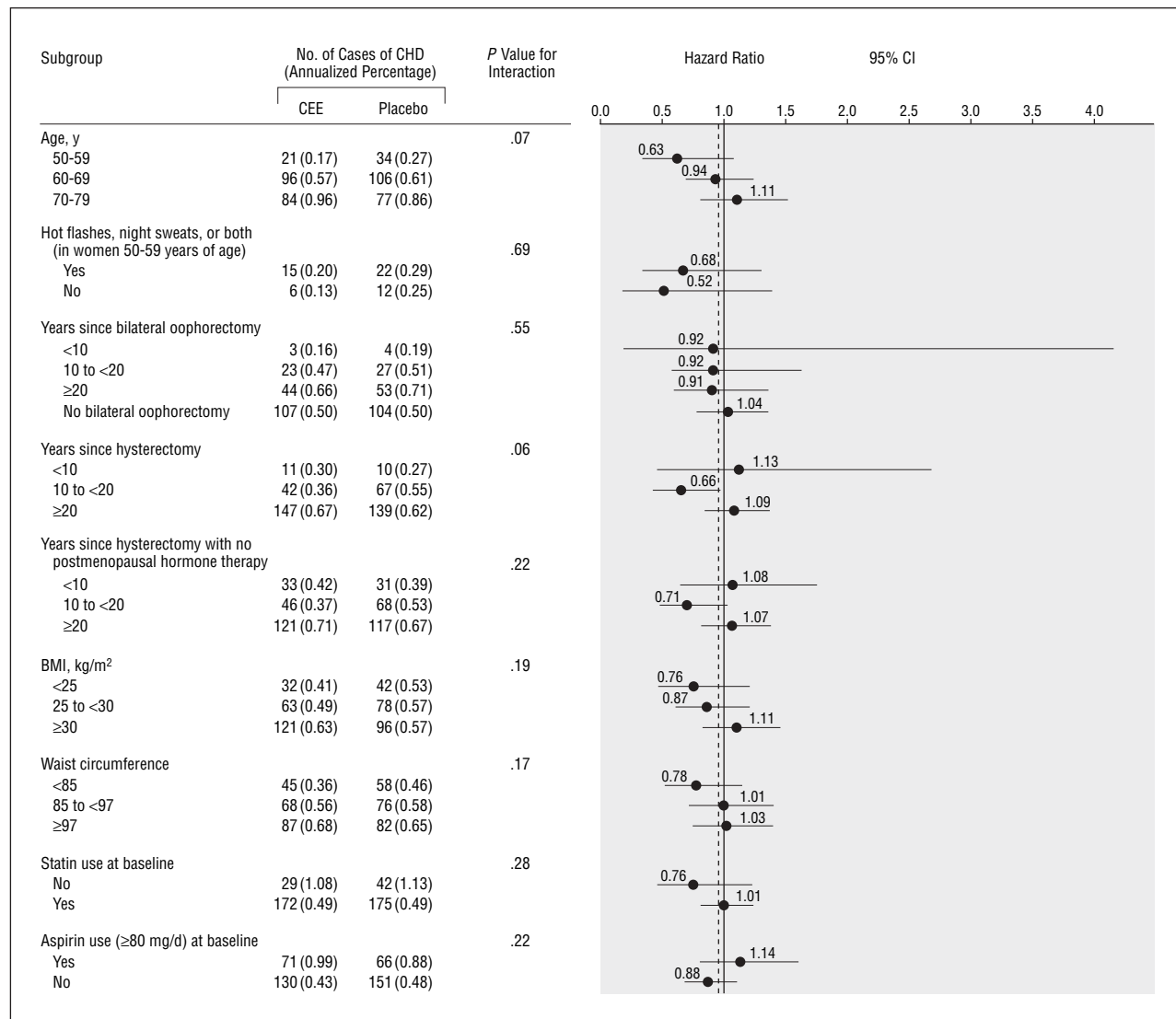


Figure 3. Risk of coronary heart disease (CHD) by treatment group assignment in various subgroups. Horizontal bars represent nominal 95% confidence intervals (CIs). The dotted vertical line represents the hazard ratio for CHD in the overall cohort. Because of missing data for some variables, numbers do not always add up to the total number of cases. BMI indicates body mass index (calculated as weight in kilograms divided by the square of height in meters); CEE, conjugated equine estrogens; and statin, hydroxymethylglutaryl coenzyme A reductase inhibitor.

difference in the risk of myocardial infarction or coronary death by age group because of the low event rate in young women. The challenges of designing an appropriate trial to address the issues of safety and efficacy in perimenopausal and early postmenopausal women are considerable, since the coronary event rate among 50- to 54-year-old women ($n=1396$) in the estrogen-alone trial was 0.21% per year. The sample size required to detect the 30% treatment effect we observed in this age group with 80% power would be 17 251, assuming equal numbers of women in the active treatment and placebo groups¹⁰ and complete adherence to study medication. Thus, the data provided by the Women's Health Initiative, although not providing all the answers one might wish, are likely to remain the basis for clinical decisions for the foreseeable future.

Coronary risk with CEE appeared greater for women with more years since hysterectomy; however, the pattern of coronary risk did not differ in women with and

without vasomotor symptoms by years since bilateral oophorectomy or since hysterectomy without postmenopausal hormone therapy. The totality of data, which is limited by the numbers of CHD events in some subgroups, does not support a conclusion concerning the relationship between time since menopause and coronary risk with CEE.

Women with higher levels of C-reactive protein at baseline were at apparent higher risk with CEE. If elevated C-reactive protein level reflects a more atherogenic milieu, one might anticipate that women with greater numbers of coronary risk factors or with prevalent cardiovascular disease would be at higher risk with CEE, which was not the case (Table 3). However, it remains possible that inflammatory factors contribute to the vascular effects of CEE through mechanisms largely independent of classic risk factors. No significant interaction with C-reactive protein was identified in the estrogen plus progestin trial.³

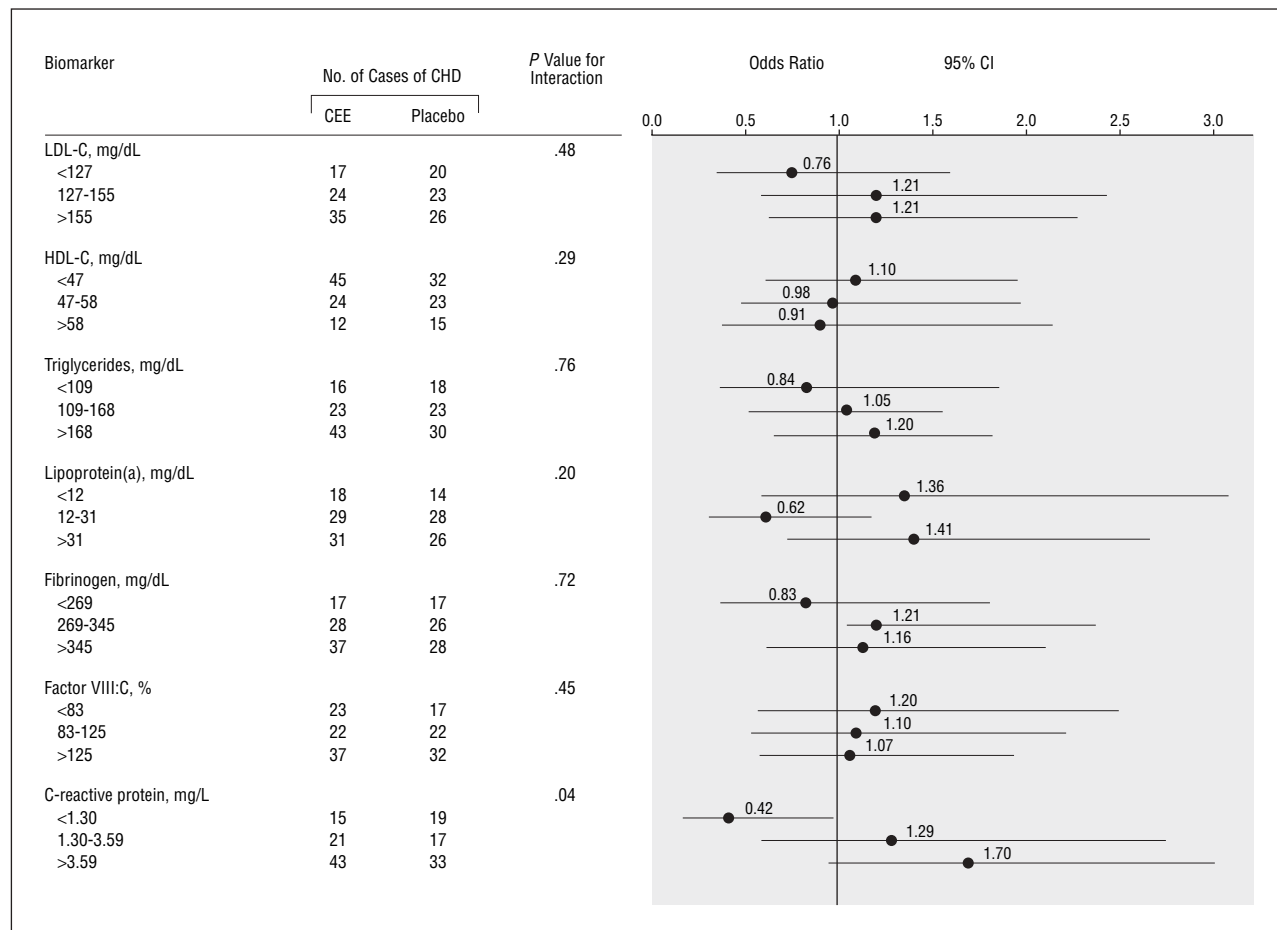


Figure 4. Conjugated equine estrogens (CEE) and coronary risk by biomarker tertile at baseline in the nested case-control study. Women were divided into 3 groups of approximately equal size on the basis of their values for each variable. Horizontal bars represent nominal 95% confidence intervals (CIs). Continuous, log-transformed biomarker values were used in the tests for interaction with treatment assignment, with a likelihood ratio statistic with 1 *df*. Odds ratios (with the placebo group within each subgroup used as the reference group) are adjusted for age, year of randomization, and presence or absence of coronary heart disease (CHD) at baseline. In addition, odds ratios for lipid variables were adjusted for statin use. To convert low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and lipoprotein(a) to micromoles per liter, multiply by 0.0357.

In the 2 Women's Health Initiative hormone trials, possible reasons for the differences in risk with CEE vs CEE with medroxyprogesterone acetate include (1) underlying characteristics of the cohorts, (2) an adverse progestin effect, (3) differential statin use during the trial, or (4) chance. At baseline, women who had undergone prior hysterectomy who joined the estrogen-alone trial were at greater risk for coronary events than were women with intact uteri who joined the estrogen plus progestin trial.⁶ Women joining the estrogen-alone trial had higher mean \pm SD body mass index (calculated as weight in kilograms divided by the square of height in meters; 30.1 ± 6.2 vs 28.5 ± 5.9) and higher prevalences of hypertension (47.7% vs 36.1%), diabetes (7.7% vs 4.4%), hypercholesterolemia (15.2% vs 12.7%), prior myocardial infarction (3.1% vs 1.8%), and coronary revascularization (2.2% vs 1.3%). The difference in coronary risk characteristics between women who had undergone prior hysterectomy and those with intact uteri is consistent with prior reports^{11,12} and is reflected in the different coronary event rates in the placebo groups: 0.56% per year in the estrogen-alone trial vs 0.33% per year in the estrogen plus progestin trial. It has been hypothesized that women with less underlying

atherosclerosis might be more likely to benefit from postmenopausal exogenous estrogen.¹³⁻¹⁵ In that case, one would expect women with intact uteri to have a more favorable response to hormones than women who have undergone hysterectomy, which is not borne out by the overall hazard ratios for coronary events in the Women's Health Initiative hormone trials or the Heart and Estrogen/progestin Replacement Study.¹⁶

A Cox regression analysis of data from the 2 hormone trials was performed to contrast the hazard ratios while adjusting for baseline risk factors. The CEE hazard ratio was significantly lower ($P=.03$) than that for CEE with medroxyprogesterone acetate in that analysis, which allowed both disease risk and hazard ratios to depend on age, ethnicity, body mass index, statin use, aspirin use, and other baseline coronary risk factors. Thus, the difference in CHD risk in the 2 trials is unlikely to be due to chance or to these baseline risk characteristics.

These differences in CHD risk may also be attributable to the addition of progestin. In the Postmenopausal Estrogen/Progestin Interventions trial, addition of progestin to CEE unfavorably affected high-density lipoprotein cholesterol and fibrinogen levels but did not alter

estrogen's effects on blood pressure, fasting glucose, insulin, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, or E-selectin levels.^{17,18} Furthermore, in primate studies, medroxyprogesterone acetate did not attenuate the coronary protection conferred by CEE.¹⁹ Nonetheless, biomarker and animal studies may not accurately predict clinical CHD risk, and progestin remains a viable explanation for the differences between the trials.

Statin prescription differed between treatment groups during the hormone trials, presumably reflecting ongoing lipid management by participants' physicians. We considered the potential confounding effect of differential statin prescription both through formal interaction testing and by including statin use as a time-dependent covariate in proportional hazards modeling and did not identify a significant impact on study results.

A similar pattern of statin prescription was observed in the estrogen plus progestin trial: among women assigned to placebo, 8.6% at year 1 and 17.3% at year 6 were taking statins. Among women assigned to CEE with medroxyprogesterone acetate, 7.9% at year 1 and 14% at year 6 were taking statins. Addition of statin use as a time-dependent covariate in Cox proportional hazards modeling had virtually no effect on the hazard ratio estimate for CHD in the estrogen plus progestin trial. Thus, the pattern of statin prescription is unlikely to account for any differences in results between the 2 trials.

The assumptions and concepts underlying putative coronary protection from postmenopausal hormone therapy have undergone strenuous reconsideration as a consequence of recent randomized trials,^{3,16,20-22} changes reflected in altered prescribing practices.²³ The views of both the medical and lay communities regarding the role of exogenous estrogen during and after menopause remain in evolution during the current paradigm shift.^{24,25}

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Author Affiliations: Department of Medicine, George Washington University, Washington, DC (Dr Hsia); Department of Family and Preventive Medicine, University of California at San Diego (Dr Langer); Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass (Dr Manson); Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pa (Dr Kuller); Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis (Dr Johnson); Department of Obstetrics and Gynecology, Wayne State University/Hutzel Women's Hospital, Detroit, Mich (Dr Hendrix), Fred Hutchinson Cancer Research Center (Ms Pettinger and Dr Prentice) and Department of Epidemiology, University of Washington, Seattle (Dr Heckbert); Department of Obstetrics and Gynecology, University of California, Irvine (Dr Greep); Department of Medicine, University of Massachusetts Medical School, Worcester (Dr Crawford); Department of Family Medicine and Center for Primary Care and Prevention, Brown University School of Medicine and Memorial Hospital of Rhode Island, Pawtucket (Dr Eaton);

Department of Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ (Dr Kostis); and University of Miami School of Medicine and Miami Veterans Administration Medical Center, Miami, Fla (Dr Caralis).

Correspondence: Judith Hsia, MD, Department of Medicine, George Washington University, 2150 Pennsylvania Ave NW, 4-414, Washington, DC 20037 (jhsia@mfa.gwu.edu).

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Announcement

Clinical Trial Registration

In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Internal Medicine* will require, as a condition of consideration for publication, registration of clinical trials in a public trials registry (such as <http://ClinicalTrials.gov> or <http://controlled-trials.com>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after March 1, 2006. For trials that began enrollment before this date, registration will be required by June 1, 2006. The trial registration number should be supplied at the time of submission.

For details about this new policy see the editorials by DeAngelis et al in the September 8, 2004 (2004;292: 1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA*.