

# Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy

## The Women's Health Initiative Randomized Controlled Trial

The Women's Health Initiative Steering Committee\*

**E**STROGEN THERAPY HAS BEEN available to postmenopausal women for more than 60 years. Proven benefits include relief of vasomotor symptoms and vaginal atrophy and prevention and treatment of osteoporosis. Observational studies primarily examining unopposed estrogen preparations have suggested a 30% to 50% reduction in coronary events,<sup>1-3</sup> and an 8% to 30% increase in breast cancer with extended use.<sup>4-6</sup>

The Women's Health Initiative (WHI) clinical trials of hormone therapy were designed in 1991-1992 using the accumulated evidence available at the time.<sup>7</sup> Two parallel randomized, double-blind, placebo-controlled clinical trials of hormone therapy were undertaken to determine whether conjugated equine estrogen (CEE) alone (for women with prior hysterectomy) or in combination with progestin (medroxyprogesterone acetate [MPA]) would reduce cardiovascular events in mostly healthy postmenopausal women. The WHI estrogen plus progestin trial was halted in July 2002 after a mean 5.2 years of follow-up because health risks exceeded benefits.<sup>8</sup> Coronary heart disease (CHD), stroke, and venous thromboembolic disease were all increased in women assigned to active treatment with estrogen plus progestin. Breast cancer was

**For editorial comment see p 1769.**

**Context** Despite decades of use and considerable research, the role of estrogen alone in preventing chronic diseases in postmenopausal women remains uncertain.

**Objective** To assess the effects on major disease incidence rates of the most commonly used postmenopausal hormone therapy in the United States.

**Design, Setting, and Participants** A randomized, double-blind, placebo-controlled disease prevention trial (the estrogen-alone component of the Women's Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. Enrolled were 10739 postmenopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity.

**Intervention** Women were randomly assigned to receive either 0.625 mg/d of conjugated equine estrogen (CEE) or placebo.

**Main Outcome Measures** The primary outcome was coronary heart disease (CHD) incidence (nonfatal myocardial infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects.

**Results** In February 2004, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided to end the intervention phase of the trial early. Estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major clinical outcomes available through February 29, 2004 (average follow-up 6.8 years), were: CHD, 0.91 (0.75-1.12) with 376 cases; breast cancer, 0.77 (0.59-1.01) with 218 cases; stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; colorectal cancer, 1.08 (0.75-1.55) with 119 cases; and hip fracture, 0.61 (0.41-0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01-1.24); total cancer, 0.93 (0.81-1.07); total fractures, 0.70 (0.63-0.79); total mortality, 1.04 (0.88-1.22), and the global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant 2 events per 10000 person-years.

**Conclusions** The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

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also increased while colorectal cancer, hip fracture, and other fractures were reduced. The lack of benefit for CHD was

\*Author/Steering Committee Information, Financial Disclosures, and WHI Investigators appear at the end of this article.

supported by the Heart and Estrogen/progestin Replacement Study (HERS), which also tested CEE plus MPA in women with known coronary artery disease at baseline.<sup>9</sup>

Despite the early termination of the WHI estrogen plus progestin trial, the WHI estrogen-alone trial was continued with ongoing careful scrutiny by an independent data and safety monitoring board (DSMB) because the health risks and benefits had not been adequately determined. In February 2004, the National Institutes of Health (NIH) decided to terminate the intervention phase of the estrogen-alone study, prior to the scheduled close-out interval of October 2004 to March 2005. This report presents the results of the estrogen-alone trial using available data through February 29, 2004, prior to notifying participants of the decision on March 1, 2004. Subsequent detailed reports will include additional outcomes occurring between the participants' last routine follow-up and the date of trial termination. An ancillary study of dementia and cognitive function will be reported separately. Two remaining components of the WHI clinical trial, testing the effects of a low-fat eating pattern and, independently, the effects of calcium plus vitamin D supplementation, are continuing.

## METHODS

### Study Population and Randomization

Detailed eligibility criteria and recruitment methods have been published.<sup>7,10</sup> Briefly, most participants were recruited by population-based direct mailing campaigns to age-eligible women, in conjunction with local and national media awareness programs. Women were eligible if they were 50 to 79 years old at initial screening, had undergone hysterectomy (thereby considered postmenopausal for enrollment purposes), and were likely to reside in the area for 3 years. Major exclusions were related to competing risks (any medical condition likely to be associated with a predicted survival of <3 years), safety (eg, prior breast cancer, other prior cancer

within the last 10 years except nonmelanoma skin cancer), adherence and retention concerns (eg, alcoholism, dementia, and transportation problems), or the clinical judgment of the participant's health care practitioner to continue hormone therapy in symptomatic or osteoporotic women. A 3-month washout period was required of women using postmenopausal hormones at initial screening. Prior to the 1997 HERS report,<sup>11</sup> which led to a change in eligibility criteria, 171 women with a history of venous thromboembolism (VTE) were enrolled. The protocol and consent forms were approved by the institutional review board for each participating institution (see the end of this article), and all women provided written informed consent.

Eligible women were randomly assigned to receive 0.625 mg/d of CEE (Premarin; Wyeth, St Davids, Pa) or a matching placebo, in equal proportions. The computerized randomization and blinding procedures have been described.<sup>12</sup> A small imbalance in the number of women in each group was a consequence of an early protocol change eliminating a CEE-alone intervention in women with a uterus.<sup>8</sup>

### Follow-up and Data Collection

Study participants were contacted by telephone 6 weeks after randomization to assess symptoms and reinforce adherence. Follow-up contacts by telephone or clinic visit occurred every 6 months, with clinic visits required annually. At each contact, adherence to study medication was assessed, and information on symptoms, safety concerns, and outcomes was collected. Electrocardiograms were recorded at baseline and at visit years 3, 6, and 9. Annual mammograms and clinical breast examinations were required; study medication was withheld if these safety procedures were not performed or the results could not be verified. Participants were followed up from the date of entry until death, loss to follow-up, or the time of a request for no further contact, regardless of their adherence to study medication. Baseline and year

1 lipid levels were measured in fasting blood specimens from a random 8.6% subsample of women. Methods for subsampling, data collection and management, and quality assurance have been published.<sup>12</sup>

### Maintenance/Discontinuation of Study Medications

During the trial, women with intolerable symptoms such as breast tenderness were managed by reducing the number of days per week that study medication was taken. Participants and study personnel remained blinded when these adjustments were made. Study medication was withheld in participants experiencing a myocardial infarction (MI), stroke, fracture or major injury involving hospitalization, surgery involving use of anesthesia, any illness resulting in immobilization for longer than 1 week, or any other severe illness in which hormone use was considered inappropriate. The decision to resume study medication after MI or stroke was left to the discretion of the clinical center, individual participant, and her health care clinician. Study medication was permanently discontinued in women who developed breast cancer; deep vein thrombosis (DVT) or pulmonary embolism (PE); malignant melanoma; meningioma; triglyceride level higher than 1000 mg/dL (>11.3 mmol/L); or who were treated by their personal health care practitioners with prescription estrogen, testosterone, or selective estrogen receptor modulators.

### Outcome Ascertainment

Designated outcome events were evaluated by review of medical records by centrally trained physician adjudicators at each clinical center who were blinded to treatment assignment and symptoms related to study medication. Final adjudication of key cardiovascular and cancer outcomes, as well as hip fractures and deaths, was performed centrally by comparably blinded WHI physician adjudicators, neurologists, or cancer coders. Centrally adjudicated results are reported when available, with locally adjudicated events

included when central adjudication has not yet been completed. Centrally adjudicated results are available for 95.7% of CHD events, 92.4% of strokes, 91.8% of PE cases, 97.2% of breast cancers, 99.2% of colorectal cancers, 89.2% of hip fractures, and 80.3% of deaths. Detailed outcome definitions and methods for ascertaining, documenting, and classifying outcomes have been published.<sup>13</sup>

**Cardiovascular Disease.** Coronary heart disease was defined as acute MI requiring overnight hospitalization, silent MI determined from serial electrocardiograms obtained every 3 years, or death due to CHD. Stroke was defined as the rapid onset of a neurologic deficit lasting more than 24 hours, supported by imaging studies in most cases (89.8% had computed tomography/magnetic resonance imaging [MRI] studies available). Venous thromboembolism was defined as PE or DVT and required clinical symptoms supported by relevant diagnostic studies. Total cardiovascular disease events include CHD, stroke, VTE, angina requiring hospitalization, coronary revascularization procedures, congestive heart failure, carotid artery disease, and peripheral vascular disease.

**Cancer.** All cancers other than non-melanoma skin cancers were confirmed by pathology reports, available for 98.2% of invasive breast, 95.0% of colorectal, and 80.6% of other cancers.

**Fractures.** All reported clinical fractures other than those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae were verified by review of radiology, MRI, or operative reports. WHI investigators did not obtain spine radiographs to ascertain subclinical vertebral fractures.

**Global Index.** A global index of risks and benefits was defined for each woman as the time to the first event among the monitored outcomes (CHD, stroke, PE, breast cancer, colorectal cancer, hip fractures, and death).<sup>14</sup>

### Statistical Power and Analyses

The trial design assumed 12375 women would need to be randomized to achieve

81% power to detect a 21% reduction in CHD rates over the projected 9-year average follow-up. This sample size would provide 65% power to detect a 20% reduction in hip fracture rates. An additional 5 years of follow-up without intervention was planned to achieve 79% power to detect a 22% increase in breast cancer risk.<sup>7</sup> Calculations based on the observed sample size and age distribution gave power estimates of 72%, 55%, and 71% for CHD, hip fracture, and breast cancer, respectively.<sup>12</sup>

Lack of adherence to study medication was summarized at each follow-up year as the cumulative proportion of randomized participants who had stopped taking study medications (dropouts) and similarly the proportion of women who began taking prescription menopausal hormones through their own health care practitioner (drop-ins), after excluding preceding deaths. Participants were classified by their most recent status with regard to study medications (stopped or not). Thus, women who temporarily stopped taking study medication were considered adherent in this analysis.

Event rate comparisons were based on the intent-to-treat principle using failure time methods. For a given outcome, the time of event was defined to be the number of days from randomization to the first postrandomization diagnosis of the designated event. For silent MIs, the date of the follow-up electrocardiogram was used as the event date. Follow-up time was censored at the time of the last documented follow-up contact or death. Comparisons of primary outcomes are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazard analyses,<sup>15</sup> stratified by age, prior disease, and randomization status in the low-fat diet trial. Cumulative hazard rates were estimated by the Kaplan-Meier method for each designated outcome.

Two forms of CIs were calculated, nominal and adjusted. This report primarily presents the nominal 95% CIs because they provide traditional esti-

mates of variability and, as such, are comparable to most other reports of hormone therapy studies. To acknowledge multiple testing issues, adjusted CIs were calculated using group sequential methods, and for secondary outcomes a Bonferroni correction based on the data and safety monitoring plan (see below). Because the trial was nearing the planned termination, the impact of the group sequential adjustment on the width of the CIs is small. The Bonferroni correction reflects the study design and trial monitoring priorities and hence may be somewhat less relevant for interpreting the trial results. Unless otherwise indicated, all CIs and *P* values are nominal. Statistical analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC) and significance was set at the .05 level.

The possibility of important subgroup effects was explored by testing for interactions in expanded Cox models. Because 23 interactions are reported, chance alone could produce a significant interaction at the .05 level for approximately 1 factor in the series. Sensitivity analyses were conducted to explore the possible impact of lack of adherence to study medications. In these "complier" analyses, the randomization assignment was preserved but follow-up for a woman was censored 6 months after she first became nonadherent (defined as taking <80% of study pills).

### Data and Safety Monitoring

Statistical monitoring boundaries were based on O'Brien-Fleming group sequential procedures<sup>16</sup> with asymmetric boundaries for benefit (1-sided .025-level upper boundary for CHD) and adverse effects (1-sided .05-level lower boundary). The adverse effect boundary for the 6 monitored outcomes of CHD, stroke, PE, hip fractures, colorectal cancer, and death from causes other than the monitored disease outcomes incorporated a Bonferroni correction. The Bonferroni correction was not applied to breast cancer because it was the primary safety outcome. Early stopping was to be

considered if a disease-specific boundary was crossed and the global index was supportive of the overall direction of CEE effects. Formal monitoring of disease rate comparisons began in the fall of 1997 with trial termination planned for March 2005. Additional aspects of the monitoring plan have been published.<sup>14</sup>

## RESULTS

### Trial Monitoring and Early Stopping

In early 2000 and again in 2001, after reviewing the data from the estrogen-alone and the estrogen plus progestin trials, the DSMB recommended that participants in both trials be informed of early increases in rates of heart dis-

ease, strokes, and blood clots in women taking active hormone pills. In 2002, with the early termination of the estrogen plus progestin trial, participants in the estrogen-alone trial were informed that no increase in breast cancer rates had been observed at that point in women taking CEE. The DSMB continued to closely monitor the estrogen-alone trial. The DSMB's review of the data for the 13th planned interim analysis through August 31, 2003, plus an unplanned analysis using data through November 30, 2003, did not lead to a consensus recommendation. None of the predefined stopping boundaries had been crossed, although the stroke comparison was approaching the adverse effect boundary.

On February 2, 2004, following subsequent reviews with additional advisors, the NIH decided to stop the intervention phase of the trial. The NIH concluded that with an average of nearly 7 years of follow-up completed, CEE does not appear to affect the risk of heart disease, the primary outcome of the study. Furthermore, the NIH found an increased risk of stroke that was similar to the risk reported from the estrogen plus progestin trial. Recognizing the risk of stroke, and the likelihood that neither cardioprotection nor breast cancer risk would be demonstrated in the remaining intervention period, the NIH deemed it unacceptable to subject healthy women in a prevention trial to this risk.<sup>17</sup> On March 1, 2004, participants were informed of the trial termination and advised to stop taking their study medication. Data available through February 29, 2004, by routine data collection are included in this report.

### Baseline Characteristics

Between 1993 and 1998, a total of 10739 women were randomized into the estrogen-alone trial. Demographic characteristics, medical history, and health behaviors of these women have been described in considerable detail.<sup>18</sup> In general, study participants were healthy and at average risk of CHD and breast cancer, although 441 (4.1%) with

**Table 1.** Baseline Demographic and Clinical Characteristics of the Women's Health Initiative Estrogen-Alone Trial Participants With Prior Hysterectomy (N = 10 739) by Randomization Assignment\*

Characteristics	CEE (n = 5310)	Placebo (n = 5429)
Age at screening, mean (SD), y	63.6 (7.3)	63.6 (7.3)
Age group at screening, y, No. (%)		
50-59	1637 (30.8)	1673 (30.8)
60-69	2387 (45.0)	2465 (45.4)
70-79	1286 (24.2)	1291 (23.8)
Race/ethnicity, No. (%)		
White	4007 (75.5)	4075 (75.1)
Black	782 (14.7)	835 (15.4)
Hispanic	322 (6.1)	333 (6.1)
American Indian	41 (0.8)	34 (0.6)
Asian/Pacific Islander	86 (1.6)	78 (1.4)
Unknown	72 (1.4)	74 (1.4)
Hormone use, No. (%)		
Never	2769 (52.2)	2770 (51.1)
Past	1871 (35.2)	1948 (35.9)
Current†	669 (12.6)	708 (13.0)
Duration of prior hormone use, y, No. (%)‡		
<5	1352 (53.2)	1412 (53.1)
5-<10	469 (18.5)	515 (19.4)
≥10	720 (28.3)	732 (27.5)
Body mass index, mean (SD)§	30.1 (6.1)	30.1 (6.2)
Body mass index, No. (%)		
<25	1110 (21.0)	1096 (20.3)
25-29	1795 (34.0)	1912 (35.5)
≥30	2376 (45.0)	2383 (44.2)
Systolic BP, mean (SD), mm Hg	130.4 (17.5)	130.2 (17.6)
Diastolic BP, mean (SD), mm Hg	76.5 (9.2)	76.5 (9.4)
Smoking, No. (%)		
Never	2723 (51.9)	2705 (50.4)
Past	1986 (37.8)	2089 (38.9)
Current	542 (10.3)	571 (10.6)
Parity, No. (%)		
Never pregnant/no term pregnancy	489 (9.3)	461 (8.5)
≥1 Term pregnancy	4779 (90.7)	4932 (91.5)
Age at first birth, y, No. (%)		
<20	1193 (28.1)	1234 (28.0)
20-29	2846 (67.0)	2914 (66.1)
≥30	210 (4.9)	260 (5.9)

Abbreviation: CEE, conjugated equine estrogen.

\*Subgroup totals may not sum to number randomized because of missing data.

†Required a 3-month washout prior to randomization.

‡Among women reporting hormone use.

§Measured as weight in kilograms divided by height in meters squared. Data available for 5281 CEE and 5391 placebo participants.

||Among women reporting ≥1 term pregnancy.

prior MI or coronary revascularization were enrolled. The intervention groups were well balanced at baseline on key demographic and disease risk factor characteristics (TABLE 1 and TABLE 2).

### Follow-up, Adherence, and Unblinding

Vital status is known for 10176 (94.8%) of randomized participants, including 580 (5.4%) known to be deceased. Over the average 6.8 years of follow-up (range, 5.7-10.7 years), only 563 women (5.2%) withdrew, were considered lost to follow-up, or had stopped providing outcomes information for more than 18 months (FIGURE 1).

At the time of study termination, 53.8% of women had already stopped taking study medication. Dropout rates exceeded design projections, particularly early on, but did not differ significantly by randomization assignment and were stable after year 1, even with the termination of the estrogen plus progestin trial (FIGURE 2). Some women initiated hormone use through their own health care clinician: 5.7% of women in the CEE group and 9.1% in the placebo group by follow-up year 6. These drop-in rates in the placebo group were also somewhat greater than expected. Reasons for initiating hormone therapy outside of the study were not captured. Unblinding of the study gynecologist to randomization assignment was infrequent, occurring for only 100 women in the CEE group and 83 in the placebo group. Per protocol, the treatment assignment was not revealed to other study staff members or the study participants.

### Intermediate Cardiovascular Disease End Points

Fasting blood lipid levels, assessed in an 8.6% subsample of women at baseline and year 1, showed a greater reduction in low-density lipoprotein cholesterol ( $-13.7\%$  vs  $-1.0\%$ ,  $P < .001$ ) and a larger increase in high-density lipoprotein cholesterol ( $15.1\%$  vs  $1.1\%$ ,  $P < .001$ ) in the CEE group compared with the placebo group. Reductions in

**Table 2.** Baseline Medical History Characteristics of the Women's Health Initiative Estrogen-Alone Trial Participants With Prior Hysterectomy (N = 10 739) by Randomization Assignment\*

Characteristics	CEE (n = 5310)	Placebo (n = 5429)
Age at hysterectomy, y, No. (%)		
<40	2100 (39.8)	2149 (39.8)
40-49	2281 (43.2)	2275 (42.2)
50-54	501 (9.5)	566 (10.5)
≥55	401 (7.6)	404 (7.5)
Bilateral oophorectomy, No. (%)	1938 (39.5)	2111 (42.0)
Medical treatment, No. (%)		
Treated for diabetes	410 (7.7)	411 (7.6)
Treated for hypertension or BP ≥140/90 mm Hg	2386 (48.0)	2387 (47.4)
Elevated cholesterol levels requiring medication	694 (14.5)	766 (15.9)
Statin use at baseline	394 (7.4)	427 (7.9)
Aspirin use (≥80 mg/d) at baseline	1030 (19.4)	1069 (19.7)
Medical history, No. (%)		
Myocardial infarction	165 (3.1)	172 (3.2)
Angina	308 (5.8)	306 (5.7)
CABG/PTCA	120 (2.3)	114 (2.1)
Stroke	76 (1.4)	92 (1.7)
DVT or PE	87 (1.6)	84 (1.5)
Female relative had breast cancer, No. (%)	893 (18.0)	870 (17.1)
Fracture at age ≥55 y, No. (%)	676 (14.0)	643 (13.2)
No. of falls in last 12 mo, No. (%)		
0	3300 (67.0)	3230 (64.8)
1	975 (19.8)	1024 (20.5)
2	422 (8.6)	478 (9.6)
≥3	231 (4.7)	255 (5.1)

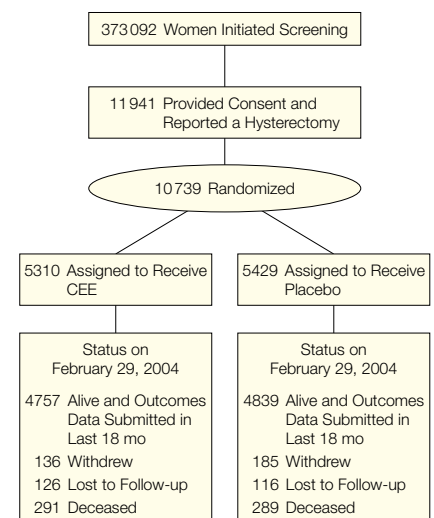
Abbreviations: BP, blood pressure; CABG/PTCA, coronary artery bypass graft/percutaneous transluminal coronary angioplasty; CEE, conjugated equine estrogen; DVT, deep vein thrombosis; PE, pulmonary embolism.  
\*Subgroup totals may not sum to number randomized because of missing data.

total cholesterol from baseline to year 1 were comparable ( $-2.3\%$  vs  $-1.4\%$ ,  $P = .41$ ). Larger increases in triglyceride levels at year 1 were observed in the CEE group than in the placebo group ( $25.0\%$  vs  $3.0\%$ ,  $P < .001$ ). Systolic blood pressure at 1 year was higher by a mean (SE) of 1.1 (0.4) mm Hg in women taking CEE than in women taking placebo ( $P = .003$ ) and remained similarly elevated throughout follow-up. Diastolic blood pressures did not differ significantly between the study groups (data not shown).

### Clinical Outcomes

**Cardiovascular Disease.** The primary outcome for this trial was the rate of CHD. The observed CHD incidence rate of 51 per 10000 person-years was 15% lower than projected in the design. No significant effect of CEE was observed on CHD rates compared with placebo

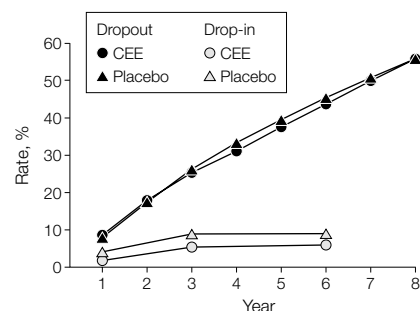
**Figure 1.** Participant Flow in the Estrogen-Alone Component of the Women's Health Initiative



CEE indicates conjugated equine estrogen.

(49 vs 54 per 10000 person-years; 9% reduction) (TABLE 3). These data rule out a reduction in CHD rates with CEE

**Figure 2.** Cumulative Drop-in and Dropout Rates by Randomization Assignment and Follow-up Duration



CEE indicates conjugated equine estrogen. Use of non-study hormones to estimate drop-ins was routinely surveyed only in follow-up years 1, 3, and 6.

of more than 25% during the trial period. The incidence of stroke was increased by 39% in the CEE group (44 vs 32 per 10000 person-years,  $z = -2.72$ ,  $P = .007$ ), which crossed the adverse effect monitoring boundary for the 14th planned interim analysis (defined as  $z = -2.69$ ). The risk of VTE, including both DVT and PE, was increased for women taking CEE (28 vs 21 per 10000 person-years; 33% increase), although only the increased rate of DVT reached statistical significance ( $P = .03$ ). Total cardiovascular disease event rates, including stroke, were 12% higher in women taking CEE (225 vs 201 per 10000 person-years,  $P = .02$ ).

**Cancer.** Invasive breast cancer, the primary safety outcome for this trial, was diagnosed at a 23% lower rate in the CEE group than in the placebo

group (26 vs 33 per 10000 person-years) and this comparison narrowly missed statistical significance ( $P = .06$ ). No significant differences were found in rates of colorectal cancer for CEE vs placebo (17 vs 16 per 10000 person-years) or total cancer (103 vs 110 per 10000 person-years) (Table 3).

**Fractures.** Use of CEE reduced the rates of fractures by 30% to 39%. Hip fracture rates were 11 vs 17 per 10000 person-years ( $P = .01$ ); clinical vertebral fractures, 11 vs 17 per 10000 person-years ( $P = .02$ ); and total osteoporotic fractures, 139 vs 195 per 10000 person-years ( $P < .001$ ) (Table 3).

**Summary Measures.** The global index of health risks and benefits was balanced overall (HR, 1.01; 95% CI, 0.91-1.12). Of the 580 reported deaths, 94.8% have been adjudicated. Use of

**Table 3.** Clinical Outcomes by Randomization Assignment

Outcomes	No. of Patients (Annualized %)		Hazard Ratio*	Nominal 95% CI	Adjusted 95% CI
	CEE (n = 5310)	Placebo (n = 5429)			
Follow-up time, mean (SD), mo	81.6 (19.3)	81.9 (19.7)	NA	NA	NA
Cardiovascular disease†					
CHD	177 (0.49)	199 (0.54)	0.91	0.75-1.12	0.72-1.15
CHD death	54 (0.15)	59 (0.16)	0.94	0.65-1.36	0.54-1.63
Nonfatal MI	132 (0.37)	153 (0.41)	0.89	0.70-1.12	0.63-1.26
Stroke	158 (0.44)	118 (0.32)	1.39	1.10-1.77	0.97-1.99
Fatal	15 (0.04)	14 (0.04)	1.13	0.54-2.34	0.38-3.36
Nonfatal	114 (0.32)	85 (0.23)	1.39	1.05-1.84	0.91-2.12
Venous thromboembolic disease	101 (0.28)	78 (0.21)	1.33	0.99-1.79	0.86-2.08
Deep vein thrombosis	77 (0.21)	54 (0.15)	1.47	1.04-2.08	0.87-2.47
Pulmonary embolism	48 (0.13)	37 (0.10)	1.34	0.87-2.06	0.70-2.55
Total cardiovascular disease	811 (2.25)	746 (2.01)	1.12	1.01-1.24	0.97-1.30
Cancer					
Invasive breast	94 (0.26)	124 (0.33)	0.77	0.59-1.01	0.57-1.06
Colorectal	61 (0.17)	58 (0.16)	1.08	0.75-1.55	0.63-1.86
Total	372 (1.03)	408 (1.10)	0.93	0.81-1.07	0.75-1.15
Fractures					
Hip	38 (0.11)	64 (0.17)	0.61	0.41-0.91	0.33-1.11
Vertebral	39 (0.11)	64 (0.17)	0.62	0.42-0.93	0.34-1.13
Total	503 (1.39)	724 (1.95)	0.70	0.63-0.79	0.59-0.83
Death					
Due to other causes‡	193 (0.53)	185 (0.50)	1.08	0.88-1.32	0.79-1.46
Total	291 (0.81)	289 (0.78)	1.04	0.88-1.22	0.81-1.32
Global index§	692 (1.92)	705 (1.90)	1.01	0.91-1.12	0.89-1.14

Abbreviations: CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; NA, not applicable.

\*From Cox proportional hazards model stratified by age, prior disease, and randomization status in the dietary modification trial.

†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 14 silent MIs. Total cardiovascular disease is limited to events requiring or during hospitalization except venous thromboembolic disease reported after January 1, 2000.

‡All deaths except those from breast or colorectal cancer, definite/probable CHD, pulmonary embolism, or cerebrovascular disease.

§The global index represents the first event for each participant from among the following: CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fracture, or death due to other causes.

CEE did not significantly affect total mortality rates or cause-specific mortality (TABLE 4).

**Time Trends**

Differences in cumulative hazards for stroke and to a lesser extent for hip fracture began to emerge early in the intervention period and persisted throughout follow-up (FIGURE 3). Cumulative breast cancer hazard rates appeared to separate beginning in year 2. Similar displays for the global index and death (FIGURE 4) reinforce the comparability of these rates across treatment groups. Tests for trends with time since

randomization were computed for all of the monitored and composite outcomes using a Cox proportional hazards model with a time-dependent treatment interaction term. Coronary heart disease was the only outcome with a statistically significant trend ( $P = .02$ ) of slightly elevated HRs in the early follow-up period that diminished over time (year 1, 1.16; year 2, 1.20; year 3, 0.89; year 4, 0.79; year 5, 1.28; year 6, 1.24, and year  $\geq 7$ , 0.42).

**Further Analyses**

Exploratory analyses were conducted to determine whether selected partici-

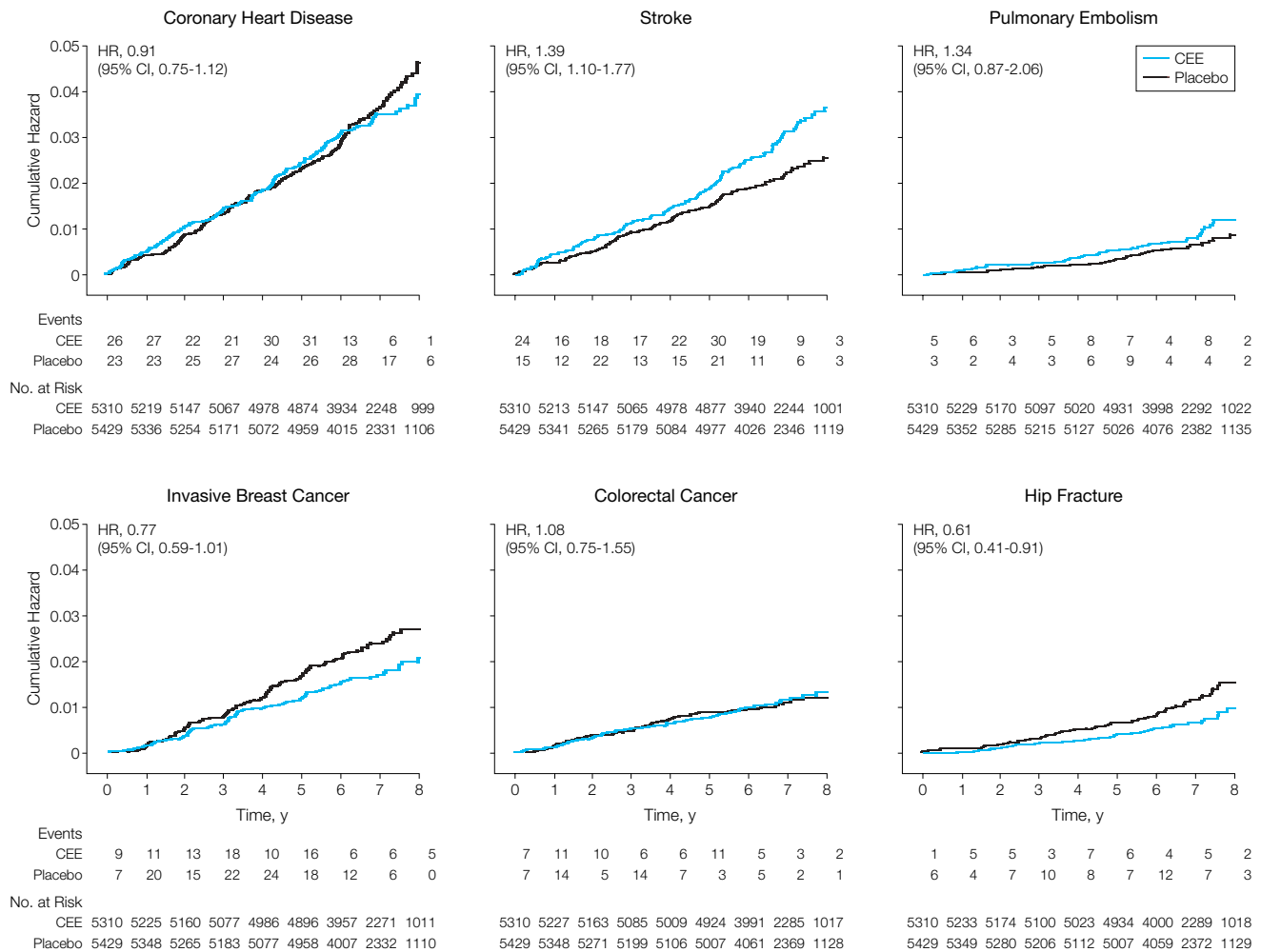
pant characteristics modified CEE effects on major clinical outcome event rates. There were no significant interactions between CEE and race/

**Table 4. Causes of Death**

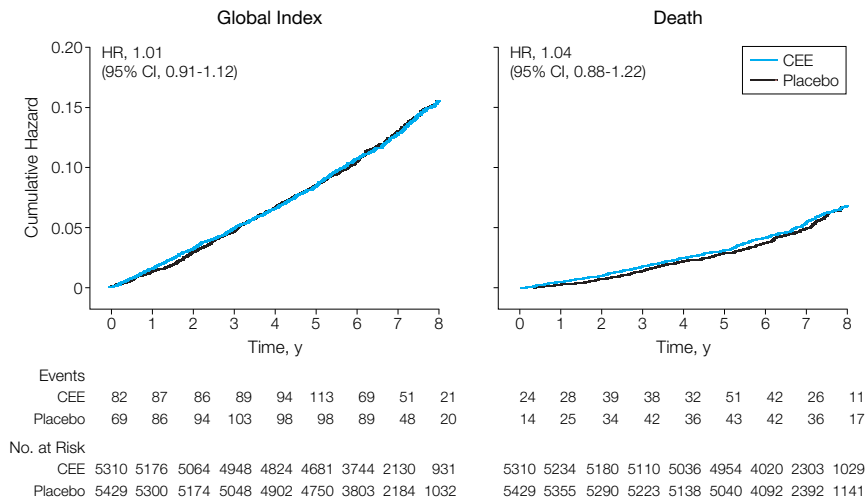
	No. (Annualized %)	
	CEE (n = 5310)	Placebo (n = 5429)
Total deaths	291 (0.81)	289 (0.78)
Adjudicated deaths	278 (0.77)	272 (0.73)
Cardiovascular	93 (0.26)	95 (0.26)
Breast cancer	4 (0.01)	8 (0.02)
Other cancer	110 (0.30)	118 (0.32)
Other known cause	51 (0.14)	38 (0.10)
Unknown cause	20 (0.06)	13 (0.04)

Abbreviation: CEE, conjugated equine estrogen.

**Figure 3. Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes**



CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8.

**Figure 4.** Kaplan-Meier Estimates of Cumulative Hazards for Global Index and Death

CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8.

ethnicity or body mass index on risk of CHD, stroke, VTE, breast cancer, colorectal cancer, hip fracture, or total osteoporotic fracture (data not shown). Of particular interest for all outcomes was age at enrollment (FIGURE 5). The only treatment  $\times$  age interaction reaching statistical significance was for colorectal cancer ( $P = .048$ ), for which increasing age was associated with increasing risk with CEE use.

The effect of prior disease on cardiovascular event rates was also evaluated. Among the 441 women enrolled with prior MI or revascularization procedures, the effect of CEE relative to placebo (33 vs 31; HR, 1.04; 95% CI, 0.63-1.71) did not differ significantly from the CEE effect in women without documented CHD (143 vs 162; HR, 0.91; 95% CI, 0.73-1.14) ( $P = .55$ ). Similarly, in 168 women reporting prior stroke, the HR for subsequent stroke (6 vs 6; HR, 1.67; 95% CI, 0.52-5.36) did not differ from the HR in women without a history of stroke (152 vs 112; HR, 1.39; 95% CI, 1.09-1.78) ( $P = .77$ ). Removing from analysis the few participants with a history of PE did not alter the hazard ratio for PE substantially (47 vs 37; HR, 1.31; 95% CI, 0.85-2.01).

Sensitivity analyses were conducted to provide an indication of the potential impact of lack of adherence to assigned study medication. Compared with the primary intent-to-treat analyses (Table 3), the "complier" models estimated greater risks of stroke (HR, 1.74), pulmonary embolism (HR, 1.99), and total mortality (HR, 1.26) but lower risks of breast cancer (HR, 0.65), hip fracture (HR, 0.48), and colorectal cancer (HR, 0.92). The HRs for CHD (HR, 0.89) and the global index (HR, 1.06) were essentially unchanged.

## COMMENT

The WHI estrogen-alone study was a large-scale, randomized, double-blind, placebo-controlled trial designed to test the effects of the most commonly used postmenopausal hormone therapy preparation in the United States<sup>19</sup> on chronic disease incidence in a diverse population of mostly healthy postmenopausal women aged 50 to 79 years. As conceived, the study had adequate power to detect moderate effects on CHD, hip fractures, and with longer-term follow-up, breast cancer among women across the broad age range relevant for disease prevention hypotheses. This trial demonstrated that

CEE increases the risk of stroke, reduces the risk of hip and other fractures, but does not significantly affect the incidence of CHD (the primary outcome) or overall mortality. A nonsignificant reduction in breast cancer incidence requires additional investigation. These observed risks and benefits of CEE for chronic disease rates appear to be balanced over an average 6.8-year follow-up period.

The lack of effect of CEE on CHD risk is substantially different from the favorable reports from observational studies that motivated this trial, and was observed despite an improvement in cholesterol levels. However, these results are consistent with several recent secondary prevention trials that showed no benefit of hormone therapy on atherosclerosis or clinical events.<sup>20-24</sup> The current study suggests that younger women who use CEE may be at reduced risk of CHD but this possible association may be due to chance.

These CHD results for CEE also differ importantly from 2 previous trials of estrogen plus progestin. In both the WHI estrogen plus progestin trial<sup>25</sup> and HERS,<sup>26</sup> the risk of CHD was significantly elevated in the first year of treatment and the cumulative effects of estrogen plus progestin never appeared beneficial. In the current study, a smaller, nonsignificant increase was observed in the first year of CEE exposure but the cumulative effect suggests a possible modest benefit with longer-term use. Potential explanations for this discrepancy include the role of progestin, differences in the study populations in baseline risk factors,<sup>18</sup> duration of intervention and follow-up time, and the role of chance.

The observed adverse effect of CEE on the risk of stroke is consistent with the risks reported by the WHI and HERS estrogen plus progestin trials.<sup>27,28</sup> In addition, the use of estradiol in women after ischemic stroke resulted in no change in mortality but a higher rate of recurrent nonfatal stroke and a suggestion of more severe functional deficits.<sup>29</sup> The small but persistent increase in systolic

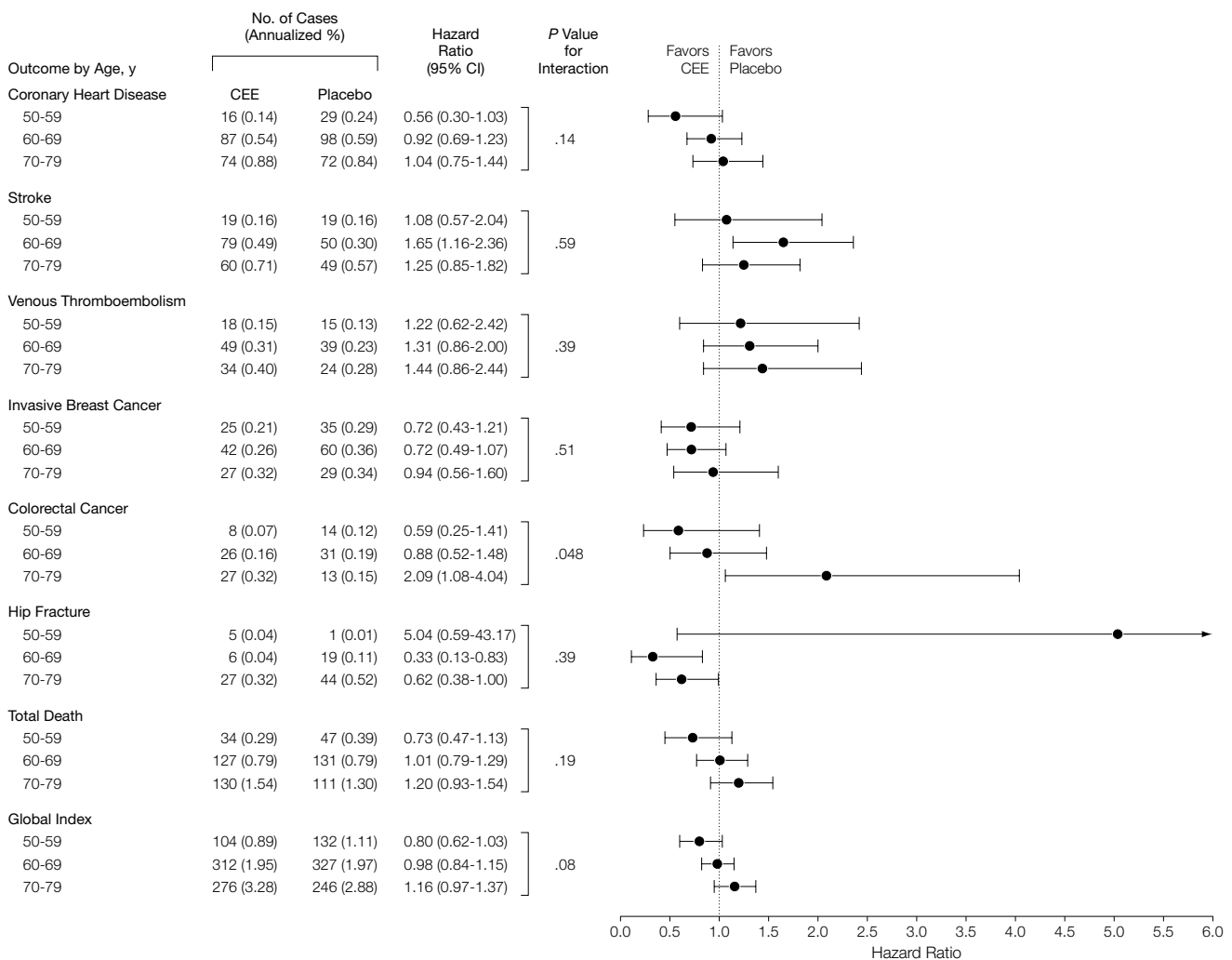
blood pressure in women taking CEE is one possible contributor to this effect because relatively small differences in systolic blood pressure have been positively associated with differences in stroke and cardiovascular disease rates.<sup>30,31</sup>

The WHI estrogen-alone trial provides strong evidence that CEE reduces the risk of hip, clinical vertebral, and other fractures. These reductions were of similar magnitude to those observed in the WHI estrogen plus progestin trial<sup>32</sup> and are consistent with findings from prior observational studies<sup>33,34</sup> and recent meta-analyses.<sup>35-37</sup>

The trend toward a reduction in breast cancer incidence was unanticipated and is opposite of that observed in the WHI estrogen plus progestin trial, which reported a 24% increased risk.<sup>38</sup> These results also appear contrary to the preponderance of observational study results,<sup>4,39</sup> including those from the recent Million Women Study.<sup>40</sup> When examining breast cancer risk by type of hormone therapy, most of these studies have reported a modest increase in breast cancer risk with estrogen alone but a greater risk for estrogen plus progestin. Still others have recently found little or no effect of estrogen alone on

breast cancer risk.<sup>41</sup> Differences in breast cancer screening between the CEE and placebo groups do not explain the observed breast cancer effects because the WHI protocol mandated annual mammography and clinical breast examinations. The possibility that diagnostic delay could account for this reduction seems remote because the effect of CEE alone on breast density is minimal.<sup>42</sup> Longer-term effects of CEE on breast cancer risk remain uncertain. Extended follow-up, as is currently planned, and analyses of breast cancer characteristics similar to those reported for the estrogen

**Figure 5.** Selected Clinical Outcomes by Participant Age and Randomization Assignment



CEE indicates conjugated equine estrogen; CI, confidence interval. Data are plotted as hazard ratios with error bars showing 95% CIs.

plus progestin study<sup>38</sup> may provide additional insight.

In preliminary subgroup analyses, the estimated HRs for CEE for several monitored outcomes, including the global index, were lower for women aged 50 to 59 years, although differences in HRs across age groups were not statistically significant. While these results suggest that CEE may be somewhat more favorable in younger than in older women, these subgroup analyses must be interpreted with caution; we cannot exclude the role of chance or limited power.

### Limitations

This trial was designed to test only one unopposed estrogen preparation at a single dose, administered orally. We cannot determine whether these results would apply to other formulations, doses, or routes of administration. Care is needed in making comparisons of these estrogen-alone trial results to those of the estrogen plus progestin trial, even though this is of considerable interest. The differences between these 2 study populations in their baseline characteristics,<sup>18,43</sup> their event rates, the length of intervention and follow-up time, and the completeness of data at this initial report are sufficient to make simple contrasts potentially misleading. More detailed analyses of these parallel trials are planned.

The high rates of discontinuation of study medications and higher than expected crossover from placebo to active hormone use are further limitations. The rate of discontinuation is less than what is usually observed in clinical practice<sup>44</sup> and was similar in the 2 groups. The somewhat higher drop-in rate in the placebo group is not explained by unblinding, which was infrequent (1.5%) and similar in the 2 groups. Sensitivity analyses suggest that the lack of adherence to assigned study medication may have diluted the CEE effects, both positive and negative, relative to what might be observed with full adherence, but it did not distort the overall balance of effects.

Lower than anticipated event rates for some outcomes, particularly CHD and

hip fractures, reduce the power relative to what was originally projected but reinforce the generally healthy status of these participants. The fact that the trial was stopped early further decreases the precision of the estimated effects. A longer intervention period may have provided stronger statistical evidence of CEE effects, particularly for CHD, for which some evidence of a trend with time was observed, and for breast cancer, for which the cumulative effect of long-term exposure remains uncertain. Additional data could have allowed for more informative subgroup analyses. Extended follow-up of these women without further intervention is planned.

### Clinical Implications

In women aged 50 to 79 years reporting a prior hysterectomy, CEE did not affect CHD rates but did increase the risk of stroke, accounting for an excess risk of 12 cases per 10000 person-years, and reduced the risk of hip fractures, resulting in 6 fewer cases per 10000 person-years. Unexpectedly, women taking CEE also appeared to be diagnosed as having breast cancer at a lower rate than women taking placebo, but the estimated 7 fewer cases per 10000 person-years did not reach statistical significance. The totality of monitored effects, as summarized in the prespecified global index, suggests an overall balance of risks and benefits and importantly no effect on total mortality.

Based on these findings, women and their health care professionals now have usable risk estimates for the benefits and harms of CEE alone. Women considering taking CEE should be counseled about an increased risk of stroke but can be reassured about no excess risk of heart disease or breast cancer for at least 6.8 years of use. At present, these data demonstrate no overall benefit of CEE for chronic disease prevention in postmenopausal women and thus argue against its use in this setting. Overall, these data support the current US Food and Drug Administration recommendations for postmenopausal women to use CEE only for menopausal symp-

toms at the smallest effective dose for the shortest possible time.<sup>45</sup>

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