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

Estrogen 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,1–3 and an 8% to 30% increase in breast cancer with extended use.4–6

The Women's Health Initiative (WHI) clinical trials of hormone therapy were designed in 1991-1992 using the accumulated evidence available at the time.7 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.8 Coronary heart disease (CHD), stroke, and venous thromboembolic disease were all increased in women assigned to active treatment with estrogen plus progestin. Breast cancer incidence was also increased while colorectal cancer, hip fracture, and other fractures were reduced. The lack of benefit for CHD was

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

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 monitor-
ning board (DSMB) because the health 
risks and benefits had not been ade-
quately 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 Oc-
tober 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 fol-
low-up and the date of trial termina-
tion. An ancillary study of dementia and 
cognitive function will be reported sepa-
rate. Two remaining components of 
the WHI clinical trial, testing the ef-
facts of a low-fat eating pattern and, in-
dependently, the effects of calcium plus 
vitamin D supplementation, are con-
tinuing.

**METHODS**

**Study Population and Randomization**

Detailed eligibility criteria and recruit-
ment methods have been published.7,10 
Briefly, most participants were re-
cruited by population-based direct mail-
ing campaigns to age-eligible women, in 
combination 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 post-
menopausal for enrollment purposes), 
and were likely to reside in the area for 
3 years. Major exclusions were related 
to competing risks (any medical condi-
tion likely to be associated with a pre-
dicted survival of \(<3\) years), safety (eg, 
prior breast cancer, or prior cancer

within the last 10 years except nonmela-
noma skin cancer), adherence and re-
tention concerns (eg, alcoholism, de-
mentia, and transportation problems), 
or the clinical judgment of the partici-
 pant’s health care practitioner to con-
tinue hormone therapy in symptom-
atic or osteoporotic women. A 3-month 
washout period was required of women 
using postmenopausal hormones at ini-
tial screening. Prior to the 1997 HERS 
report,11 which led to a change in eligi-
bility criteria, 171 women with a his-
tory of venous thromboembolism (VTE) 
were enrolled. The protocol and con-
sent forms were approved by the insti-
tutional review board for each partici-
pating institution (see the end of this 
article), and all women provided writ-
ten informed consent.

Eligible women were randomly as-
signed to receive 0.625 mg/d of CEE 
(Premarin; Wyeth, St Davids, Pa) or a 
matching placebo, in equal propor-
tions. The computerized randomiza-
tion and blinding procedures have been 
described.12 A small imbalance in the 
number of women in each group was 
a consequence of an early protocol 
change eliminating a CEE-alone inter-
tention in women with a uterus.8

**Follow-up and Data Collection**

Study participants were contacted by 
telephone 6 weeks after randomiza-
tion to assess symptoms and reinforce 
adherence. Follow-up contacts by tele-
phone or clinic visit occurred every 6 
months, with clinic visits required an-
ually. At each contact, adherence to 
study medication was assessed, and in-
formation on symptoms, safety con-
cerns, 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. Par-

cipants 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 sub-
sampling, data collection and manage-
ment, and quality assurance have been 
published.12

**Maintenance/Discontinuation of 
Study Medications**

During the trial, women with intoler-
able 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 partici-
pants experiencing a myocardial in-
farction (MI), stroke, fracture or major in-
jury 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 cen-
ter, individual participant, and her health 
care clinician. Study medication was per-
manently discontinued in women who 

developed breast cancer; deep vein 
thrombosis (DVT) or pulmonary em-
bolism (PE); malignant melanoma; me-
ningioma; triglyceride level higher than 

1000 mg/dL (>11.3 mmol/L); or who 

were treated by their personal health care 

practitioners with prescription estro-
gen, testosterone, or selective estrogen 

receptor modulators.

**Outcome Ascertainment**

Designated outcome events were evalu-
ated by review of medical records by 
centrally trained physician adjudica-
tors at each clinical center who were 
blinded to treatment assignment and 
symptoms related to study medica-
tion. Final adjudication of key cardio-
vascular and cancer outcomes, as well 
as hip fractures and deaths, was per-
formed centrally by comparably blinded 

WHI physician adjudicators, neurolo-
gists, or cancer coders. Centrally adju-
dicated results are reported when avail-
able, with locally adjudicated events
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. 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.

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, 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 estimates 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 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
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 disease, 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. 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. In general, study participants were healthy and at average risk of CHD and breast cancer, although 441 (4.1%) with
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 10,176 (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 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 10,000 person-years was 15% lower than projected in the design. No significant effect of CEE was observed on CHD rates compared with placebo.

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(49 vs 54 per 10000 person-years; 9% reduction) (TABLE 3). These data rule out a reduction in CHD rates with CEE 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 17 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.

### Table 3. Clinical Outcomes by Randomization Assignment

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

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 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 participant characteristics modified CEE effects on major clinical outcome event rates. There were no significant interactions between CEE and race/ethnicity, body mass index, and education level. For breast cancer incidence, there were significant race interactions, with the CEE effect being more pronounced among African Americans (HR, 1.24, and year 1, 1.24; 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).

**Table 4. Causes of Death**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CEE (n = 5310)</th>
<th>Placebo (n = 5429)</th>
<th>% (n)</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>291 (0.81)</td>
<td>289 (0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjudicated deaths</td>
<td>278 (0.77)</td>
<td>272 (0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>93 (0.26)</td>
<td>95 (0.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4 (0.01)</td>
<td>8 (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cancer</td>
<td>110 (0.30)</td>
<td>118 (0.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other known cause</td>
<td>51 (0.14)</td>
<td>38 (0.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>20 (0.06)</td>
<td>13 (0.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CEE, conjugated equine estrogen.

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

CCE 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.

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Of particular interest for all outcomes was age at enrollment (FIGURE 5). The only treatment × age interaction reaching statistical significance was for colorectal cancer (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 CEE effect in women without documented CHD (143 vs 162; HR, 0.91; 95% CI, 0.73-1.14) (P = .55). In 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 States15 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.20-24 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 trial25 and HERS,26 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,18 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.27,28 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.29 The small but persistent increase in systolic tension 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 × age interaction reaching statistical significance was for colorectal cancer (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 CEE effect in women without documented CHD (143 vs 162; HR, 0.91; 95% CI, 0.73-1.14) (P = .55). In 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 States15 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.

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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.30,31

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 trial32 and are consistent with findings from prior observational studies33,34 and recent meta-analyses.35-37

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

<table>
<thead>
<tr>
<th>Outcome by Age, y</th>
<th>No. of Cases (Annualized %)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>CEE</td>
<td>Placebo</td>
<td>Coronary Heart Disease</td>
<td>50-59</td>
<td>16 (0.14)</td>
</tr>
<tr>
<td>Stroke</td>
<td>50-59</td>
<td>19 (0.16)</td>
<td>19 (0.16)</td>
<td>1.08 (0.57-2.04)</td>
<td>0.59</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>50-59</td>
<td>18 (0.15)</td>
<td>15 (0.13)</td>
<td>1.22 (0.62-2.42)</td>
<td>0.39</td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td>50-59</td>
<td>25 (0.21)</td>
<td>35 (0.29)</td>
<td>0.72 (0.43-1.21)</td>
<td>0.51</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>50-59</td>
<td>8 (0.07)</td>
<td>14 (0.12)</td>
<td>0.59 (0.25-1.41)</td>
<td>0.048</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>50-59</td>
<td>5 (0.04)</td>
<td>1 (0.01)</td>
<td>5.04 (0.59-43.17)</td>
<td>0.39</td>
</tr>
<tr>
<td>Total Death</td>
<td>50-59</td>
<td>34 (0.29)</td>
<td>47 (0.39)</td>
<td>0.73 (0.47-1.13)</td>
<td>0.19</td>
</tr>
<tr>
<td>Global Index</td>
<td>50-59</td>
<td>104 (0.89)</td>
<td>132 (1.11)</td>
<td>0.80 (0.62-1.03)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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

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plus progestin study\textsuperscript{39} 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,\textsuperscript{18,43} their adherence, but it did not distort the overall balance of effects.

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\textsuperscript{44} and was similar in the 2 groups. The somewhat higher drop-in rate in the placebo group is 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 symptoms at the smallest effective dose for the shortest possible time.\textsuperscript{45}

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4. Dupont WD, Page DL. Menopausal estrogen replacement therapy...