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Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings from the WHI Observational Study

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Women's Health Initiative Investigators: A full listing of Women's Health Initiative investigators can be found at http://whiscience.org/publications/WHI_investigators_longlist

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Abstract

Objective—Research comparing hormone therapy (HT) doses, regimens, and routes of delivery in relation to cardiovascular disease (CVD) outcomes have been limited. This study directly compared different estrogen doses, routes of delivery, and HT formulations in postmenopausal women in relation to the risk of coronary heart disease (CHD), stroke, CVD mortality, total CVD, and all-cause mortality.

Methods—The Women's Health Initiative Observational Study (WHI-OS) is a multi-center prospective cohort study conducted at 40 US sites. Analyses included 93,676 postmenopausal women, aged 50-79 years at study entry and recruited September 1994 - December 1998, with annual follow-up through August 14, 2009.

Results—Average follow-up was 10.4 years. In direct comparisons, oral estradiol was associated with lower hazard ratios (HRs) for stroke than oral conjugated equine estrogens (CEE) (HR 0.64; 95% CI 0.40, 1.02), but statistical power was limited. Similarly, transdermal estradiol was associated with a moderate but non-significant lower risk of CHD compared to oral CEE (HR 0.63; 95% CI 0.37, 1.06). For other outcomes, comparisons revealed no appreciable differences by estrogen doses, formulations, or routes of delivery. Absolute risks of CVD events and all-cause mortality were markedly lower in younger, compared to older, women.

Conclusion—In direct comparisons, various HT doses and regimens were associated with similar rates of cardiovascular events and all-cause mortality. However, oral estradiol may be associated with a lower risk of stroke and transdermal estradiol with a lower risk of CHD, compared to conventional-dose oral CEE. Additional research is needed to confirm these hypotheses.

Keywords

Menopause Hormone Therapy; Cardiovascular disease; Stroke

INTRODUCTION

In 2002 the Women's Health Initiative randomized clinical trial (WHI-CT) of oral estrogen plus progestin was stopped three years early due to an unfavorable balance of health benefits and risks when hormone therapy (HT) was used for chronic disease prevention.[1] The WHI estrogen-alone trial also failed to demonstrate that treatment benefits exceeded risks under these conditions.[2] The HT prescribing guidelines of several professional organizations were revised to recommend the lowest effective HT dose for the shortest duration of time directed primarily at vasomotor symptom management, rather than chronic disease prevention.[3-5] As women continue to use HT for symptom management, the comparative safety of lower estrogen dosing, different formulations, and alternative routes of delivery with regard to cardiovascular disease (CVD) outcomes deserves further study. New lower-dose estrogens that can be administered orally or transdermally are now available and are being increasingly used, but research on these regimens has been limited. Randomized clinical trial comparisons of differing HT regimens and clinical CVD outcomes are not available. In addition, previous observational studies have not been large enough, or have not collected sufficiently detailed histories of HT use, to provide head-to-head comparisons of different estrogen doses, formulations, and routes of delivery with respect to CVD events.

Hypothetically, lower estrogen dose HT could be safer due to lower dose-related adverse CVD effects. Further, transdermal HT delivery avoids the "first pass" liver metabolism which increases serum coagulation factors, triglycerides, C-reactive protein, and a host of other factors; it also provides a more physiologic ratio of estradiol to estrone.[6-9] The health effects of the addition of progestogens, used in combination HT for women with an intact uterus, have only recently been compared to estrogen-alone with respect to coronary heart disease (CHD), stroke, and other health outcomes. For example, CVD outcomes from the WHI estrogen-alone trial showed no increased risk of myocardial infarction[10] whereas the WHI-CT of estrogen plus progestin demonstrated an overall increase in risk of CVD.[11] This has led to speculation that the addition of a progestational agent to HT is a contributing factor for CVD risk.

While both synthetic and bioidentical estradiol are effective for treating vasomotor symptoms, there are no data comparing these formulations in relation to CVD outcomes. Conjugated equine estrogens (CEE) have a complex composition with multiple biologically active estrogens and related steroids: estrone sulfate is believed to be the major active component. Whether there are differences in CVD outcomes related to CEE vs. estradiol, possibly related to differences in pharmacodynamic estrogen receptor affinity, metabolism, or other variables, has been suggested but has not been well explored.[12,13]

Several studies have demonstrated an elevated risk of CVD within the first 1-2 years of HT initiation.[1,5,11] Although we updated HT use during follow up, the observational nature of the present study did not allow for a detailed examination of this relationship because many women had long-term use before enrollment. We did not include nonusers of HT in our analyses because of known confounding factors that influence the decision to use HT[14] and because our analyses were intended to offer insight into how alternative HT formulations compare to conventional-dose oral CEE in terms of CVD outcomes. Using data from the large-scale WHI Observational Study (WHI-OS) of 93,676 postmenopausal women, we performed direct comparisons between different estrogen doses, formulations, and routes of delivery and the risk of major CHD, stroke, CVD mortality, total CVD (major CHD, stroke, CVD mortality), as well as all-cause mortality. Further we analyzed the results by time since menopause (<10 vs >10 years since menopause onset) and duration of HT use (<5 years vs >5 years) to determine whether the results varied by these factors.

METHODS

The WHI-OS is a large multi-center prospective cohort study conducted at 40 US sites. The details of the scientific rationale, eligibility criteria, and design of the WHI-OS have been previously published.[15] Briefly, 93,676 postmenopausal women with and without a uterus, aged 50–79 years were recruited between September 1994 and December 1998, with clinic visits at baseline and 3 years. Annual follow up by mailed self-administered questionnaires included detailed assessments of HT medications and collection of information on medical and lifestyle risk factors and incident clinical events. CVD events were confirmed by medical record review. The present analyses include follow up through August 14, 2009. Data were uniformly collected from participants according to a standardized institutional review board-approved protocol by trained study staff. All participants provided written informed consent for this research study at the time of enrollment.

As in previously published WHI research,[10] major CHD was defined as non-fatal clinical myocardial infarction (MI) or death due to CHD. CVD and mortality outcomes were confirmed by physician adjudicators. Stroke was defined as the rapid onset of a neurologic deficit lasting more than 24 hours, supported by imaging studies. Total CVD included major CHD, stroke, and CVD mortality. Venous thromboembolism was not included due to the

absence of medical record confirmation of this outcome in WHI-OS. HT oral conjugated estrogen (CEE) doses were defined as: low-dose CEE < 0.625 mg; conventional-dose CEE dose = 0.625 mg; and high-dose CEE > 0.625 mg. Oral estrogen formulation categories included oral estradiol and oral CEE. Oral estrogen plus progestogen (E+P) users included the formulations of both oral CEE and oral estradiol with a progestin or progesterone. Transdermal estrogen categorization included all dose formulations, as well as the use of concomitant oral progestin or progesterone among women with an intact uterus.

Statistical Analysis

Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals for different doses, routes of delivery, and formulations of HT as a time-varying exposure in relation to CVD outcomes, compared directly to conventional-dose oral CEE. Time to each CVD outcome was computed from date of enrollment to date of first CVD outcome event, and censored defined as excluded from further follow-up by date of last study follow-up or August 14, 2009, whichever occurred first. Follow up data on HT was collected on the annual study questionnaires, with a mean follow-up time of 10.4 years. For each follow-up year, the type of hormone used was categorized as non-user, estradiol, transdermal, oral low-dose CEE, oral conventional-dose CEE, conventional-dose CEE alone, E+P, and other. A variable for separate progestin or progesterone use was also created and adjusted for the analysis. All analyses were stratified by baseline 5-year age intervals and history of CVD, and adjusted for age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, Other), and smoking (never, former, current). Variables considered as potential confounders or effect modifiers were included as covariates in the model, including body mass index (BMI) categories (<25, 25-<30, ≥30), BMI (linear), quartiles of total recreational physical activity, hypertension (never, untreated, treated), treated diabetes (no,yes), high cholesterol requiring medication or current lipid lowering medication use (no,yes), hysterectomy (no,yes), oophorectomy (no, partial, bilateral), educational attainment, and household income. Tests of the proportional hazards assumption were conducted by testing interaction terms of hormone therapy (HT) exposure, separately by dose and formulation, with time to the event or censoring for the five outcomes (major CHD, stroke, total CVD, CVD mortality, and all-cause mortality). All analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina), and all p-values were 2-sided tests and values less than 0.05 were considered statistically significant.

RESULTS

Table 1 summarizes the demographic characteristics of the cohort at baseline (study enrollment), stratified by the comparison groups according to dose of CEE, HT formulation, and route of delivery. Mean duration of follow up for the WHI-OS in these analyses was 10.4 years.

At baseline, 38,024 women (41% of the WHI-OS participants) had never used HT and 13,931 (15%) reported past use at baseline and were excluded from this analysis. Among the women currently using a CEE formulation, 2,149 (7%) were on low-dose CEE, 3,396 (11%) were on high dose CEE, and the remainder (24,399 [82%]) were on conventional-dose CEE. There were 2,187 women using transdermal estrogen. The mean age at enrollment was higher for women on low dose CEE, 65.3 (7.1), and lowest at in the transdermal estradiol users, 60.1 (6.6) years. Across categories of HT dose, formulation, and route of delivery, only small differences in baseline characteristics were observed.

The absolute risk of CVD events with conventional dose HT with or without progestin or progesterone in women stratified by years since menopause is presented in figure 1. Overall,

the absolute risk of CVD in younger women with close proximity to menopause was markedly lower than for women distant from menopause. The test for the proportional hazards assumption was not violated.

Direct Comparisons By Route of Delivery

Direct comparison of transdermal HT to oral conventional-dose CEE did not demonstrate significant differences for any of the CVD outcomes (Table 2). However, there was a suggestion of lower risk of major CHD for transdermal estrogen use, as compared to conventional-dose oral estrogen, after adjustment for age, sociodemographic, lifestyle, and vascular risk factors (HR 0.63; 95% CI 0.37, 1.06). This possible lower risk remained consistent within strata of years since menopause and duration of use (data not shown). Statistical power for direct comparisons by route of delivery and time since menopause or years of use, however, was limited.

Overall, the transdermal route of delivery was also associated with a nonsignificantly lower risk of stroke and total CVD compared to oral conventional-dose CEE (RR 0.87, 95% CI 0.55-1.38 and RR 0.82, 95% CI 0.59-1.14, respectively), but risks for CVD mortality and all-cause mortality were similar to those for CEE (Table 2).

Direct Comparisons By Oral HT Dose

Women who used oral low dose HT had non-significantly lower rates of CHD, total CVD and CVD mortality after multivariable adjustment, compared to women who used oral conventional-dose HT. This was not observed for stroke or all-cause mortality, however. (Table 2)

Direct Comparisons By HT Formulation

Analysis by estrogen type (estradiol vs. CEE), indicated that oral estradiol may be associated with a lower risk of stroke than conventional-dose oral CEE (HR 0.64; 95% CI 0.40, 1.02), but the differences were not statistically significant. (Table 3) No significant differences were seen for other CVD events when directly comparing these formulations or when comparing combined E+P formulations with E-alone. In addition, results for these and other analyses did not differ substantially when stratified by number of years since menopause onset or duration of HT use (data not shown), but statistical power for such analyses was limited.

DISCUSSION

Our results indicate that CVD risk did not differ appreciably among women using different formulations, doses, and routes of administration of estrogen in comparison with conventional-dose oral CEE dose. Although similar rates were observed for most outcomes, oral estradiol may be associated with a lower risk of stroke and transdermal HT and low-dose oral CEE may be linked to a lower risk of CHD, compared to conventional-dose oral CEE. The possibility that alternative formulation, doses, and routes of delivery may pose a lower risk of stroke and CHD than conventional-dose oral CEE is an important hypothesis that warrants confirmation in additional studies. Overall absolute risk of CVD and adverse events in younger women was much lower as compared to older women.

Our study is one of the first to provide head-to-head comparisons between the transdermal route of delivery compared to conventional-dose oral CEE in terms of CVD outcomes. Although we found no statistically significant differences between these regimens for CVD outcomes, there was a suggestion of more favorable findings for CHD with transdermal therapy. Additional research is needed to confirm these findings, in view of the limited

statistical power for these analyses. To date, large-scale randomized controlled trials of different HT formulations and risk of CVD events have not been conducted.

Our data adds to the emerging evidence suggesting that transdermal estrogen delivery may have advantages in minimizing the risk of CVD events associated with HT. There is a recent observational study of over 80,000 women reported that oral but not transdermal hormone therapy carried an increased risk of stroke.[16]

Transdermal treatments avoid the first-pass hepatic metabolism associated with an increase in thrombosis, although risks may be dose-dependent. The UK General Practice Research database found that the risk of stroke did not significantly increase with low dose transdermal estradiol (0.05 mg or lower dose formulation), in contrast to an increased risk with higher transdermal doses as well as oral.[17] We did not have sufficient power to stratify transdermal regimens by dose in the current study.

The timing of HT initiation in relation to proximity to menopause has been recognized as a potentially important predictor of CVD outcomes. This “timing hypothesis” has been bolstered by observational studies and by some of the recent analyses from the WHI-CT showing that women who initiate HT closer to the menopause transition tend to have more favorable CHD outcomes with HT than those initiating HT late in menopause.[18] Although we found similar HRs in younger and older women, our statistical power to address these issues was limited. Two recent clinical trials are addressing the timing of HT initiation in relation to atherosclerosis progression, but they are not large enough to assess clinical CVD events.[19,20]

The strengths of our study include the large, diverse, and well-characterized study population with a broad distribution of HT doses and formulations. In addition, all CVD events and deaths were physician-adjudicated. Information was available on a large number of potential confounding factors, including traditional CVD risk factors, measured BMI, physical activity, other lifestyle factors, and socioeconomic status (educational attainment and household income), which in addition to age were included as covariates in the model.

The limitations of our study include the observational design that precludes causal inference. In view of the observational study design, we cannot exclude the possibility that confounding and selection factors related to the choice of HT formulation may have contributed to the CVD risk reductions. A key difference between the WHI-OS and WHI-CT, however, is that many of the women in WHI-OS began HT closer to the onset of menopause, which may be less likely to be precipitate CVD events than HT initiated in late menopause. In support of this, our current study results are generally concordant with the findings in the younger age groups studied in the WHI-CT. Another limitation is that we could not include venous thromboembolic events in our analyses due to the absence of medical record confirmation of this outcome in WHI-OS, which may have led to underestimates of total CVD risk with HT. Moreover, only a small percentage of women were using transdermal or low-dose estrogen, so the statistical power to assess these associations and to fully disentangle differences due to formulation vs dose was limited. Finally, because transdermal and low-dose estrogen are relatively newer HT formulations, their use may be a surrogate for unmeasured confounding health variables associated with lower CVD rates, such as type of prescribing healthcare provider, healthcare system or other health habits or attributes of the subjects.

We recognize that our observational cohort may underestimate HT-related CVD risk by missing events during the first few years of HT initiation, for women who began HT prior to enrollment into the WHI study. Previous randomized studies have reported an increased CVD risk with HT use that is divergent from observational results.[1,5,11,21] With regards to

stroke, randomized trials and observational studies have been concordant, showing an overall increased risk with HT.[3,5] Our study thus offers further insight into stroke risk based on findings according to estrogen formulation and route of delivery.

CONCLUSION

Our results suggest that in women using HT, the dose, formulation, and route of delivery are not associated with substantially different risks of CVD outcomes. However, transdermal and oral estradiol may be associated with lower CHD and stroke risk, respectively, as compared to conventional-dose oral CEE. Results for low-dose oral CEE also appeared more favorable than for conventional-dose oral CEE for some CVD events, although the differences were not statistically significant. Our data support a growing body of literature that suggests that the transdermal route of delivery and/or lower doses of estrogen may avoid the excess risk of certain CVD events associated with HT. Despite our current findings, systemic HT should be used only for menopausal symptom management or, in selected women, prevention of osteoporosis and not for CVD prevention, given its complex balance of benefits and risks. However, these results are potentially relevant to a very large population of women transitioning through menopause who require HT for symptom control. Additional research to confirm or refute the comparative safety of diverse HT options is needed.

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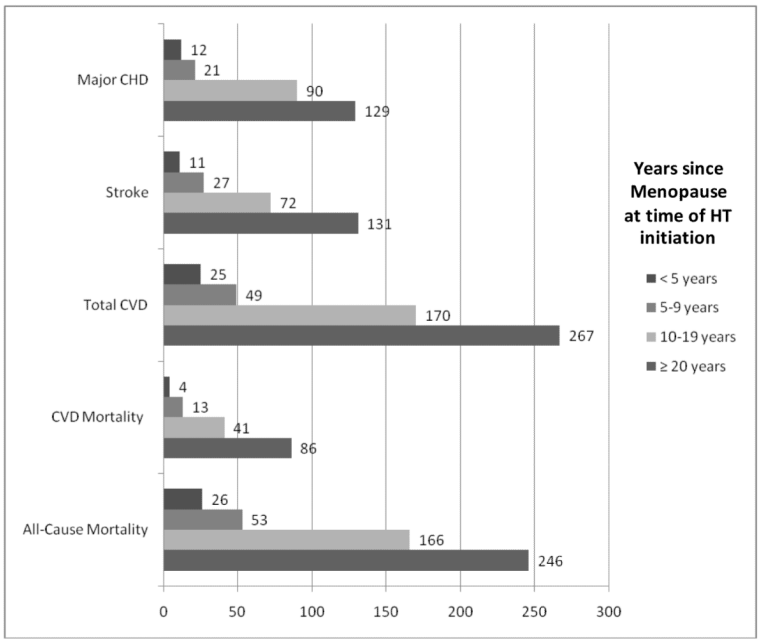

Figure 1.

Absolute Risk among women using Conventional dose CEE with or without Progestin/ progesterone: Cases per 10,000 person-years during the first 5 years of follow-up

Table 1

Demographic Characteristics by Hormone Therapy Dose and Formulation

	Dose			Formulation			Route
	Low-dose CEE* (n=2,149)	**Conventional-dose CEE+ (n=24,399)**	**High-dose CEE# (n=3,396)**	**Oral E+P** (n=13,208)**	**Oral CEE-alone (n=16,508)**	**Oral Estradiol (n=3,024)**	**Transdermal Estradiol (n=2,187)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Age at screening, mean (SD)	65.3 (7.1)	62.3 (7.0)	60.8 (7.1)	61.0 (6.7)	63.5 (7.2)	60.2 (7.0)	60.1 (6.6)
Age at menopause, years, mean (SD)	48.0 (6.9)	47.9 (6.5)	44.2 (7.0)	50.5 (4.7)	45.0 (7.0)	47.8 (6.3)	47.1 (6.7)
Race/ethnicity							
White	1897 (88.3)	21150 (86.7)	2967 (87.4)	11763 (89.1)	14013 (84.9)	2650 (87.6)	1898 (86.8)
Black	66 (3.1)	1253 (5.1)	206 (6.1)	390 (3.0)	1141 (6.9)	143 (4.7)	154 (7.0)
Hispanic	47 (2.2)	851 (3.5)	116 (3.4)	386 (2.9)	637 (3.9)	106 (3.5)	68 (3.1)
American Indian	7 (0.3)	81 (0.3)	19 (0.6)	34 (0.3)	75 (0.5)	14 (0.5)	9 (0.4)
Asian/Pacific Islander	106 (4.9)	787 (3.2)	47 (1.4)	484 (3.7)	450 (2.7)	74 (2.4)	27 (1.2)
Unknown	26 (1.2)	277 (1.1)	41 (1.2)	151 (1.1)	192 (1.2)	37 (1.2)	31 (1.4)
Education							
0-8 years	12 (0.6)	258 (1.1)	26 (0.8)	85 (0.6)	213 (1.3)	21 (0.7)	7 (0.3)
Some high school	41 (1.9)	572 (2.4)	100 (3.0)	187 (1.4)	527 (3.2)	68 (2.3)	39 (1.8)
High school diploma/GED	282 (13.2)	3449 (14.2)	539 (16.0)	1472 (11.2)	2777 (17.0)	410 (13.6)	272 (12.5)
School after high school	773 (36.3)	8595 (35.5)	1436 (42.6)	4145 (31.6)	6593 (40.3)	1095 (36.5)	876 (40.3)
College degree or higher	1023 (48.0)	11344 (46.8)	1267 (37.6)	7224 (55.1)	6270 (38.3)	1410 (46.9)	979 (45.1)
Household income							
< $10,000	28 (1.4)	611 (2.7)	96 (3.0)	211 (1.7)	527 (3.4)	53 (1.9)	39 (1.9)
$10,000 - $19,999	179 (9.0)	1833 (8.0)	262 (8.2)	716 (5.8)	1548 (10.0)	198 (7.0)	121 (5.9)
$20,000 - $34,999	449 (22.5)	4676 (20.4)	673 (21.0)	2152 (17.3)	3632 (23.5)	531 (18.6)	386 (18.7)
$35,000 - $49,999	441 (22.1)	4754 (20.8)	695 (21.7)	2480 (20.0)	3366 (21.8)	560 (19.7)	412 (20.0)
$50,000 - $74,999	436 (21.9)	5235 (22.9)	702 (21.9)	3045 (24.5)	3265 (21.1)	682 (23.9)	512 (24.9)
≥ $75,000	462 (23.2)	5777 (25.2)	776 (24.2)	3809 (30.7)	3122 (20.2)	824 (28.9)	590 (28.6)
Body-mass index (kg/m2), mean (SD)	25.8 (4.7)	26.5 (5.4)	27.1 (5.7)	25.9 (5.2)	27.1 (5.5)	26.4 (5.1)	26.6 (5.2)
Smoking status							
Never	1079 (51.0)	12045 (50.0)	1615 (48.1)	6260 (48.1)	8375 (51.4)	1484 (49.6)	1045 (48.4)
Past	945 (44.7)	10804 (44.9)	1483 (44.2)	6079 (46.7)	7038 (43.2)	1341 (44.8)	1000 (46.3)
Current	90 (4.3)	1234 (5.1)	258 (7.7)	683 (5.2)	891 (5.5)	165 (5.5)	113 (5.2)
Total physical activity (MET-hrs/wk), mean (SD)	15.3 (15.0)	14.6 (14.6)	12.9 (14.4)	15.6 (15.1)	13.6 (14.2)	14.9 (14.2)	14.5 (14.3)
Diabetes ever	86 (4.0)	985 (4.0)	145 (4.3)	392 (3.0)	818 (5.0)	96 (3.2)	95 (4.3)
History of hypertension							
Untreated	136 (6.4)	1734 (7.2)	246 (7.4)	841 (6.5)	1272 (7.8)	234 (7.8)	156 (7.2)

	Dose			Formulation			Route
	Low-dose CEE* (n=2,149)	**Conventional-dose CEE+ (n=24,399)**	**High-dose CEE# (n=3,396)**	**Oral E+P** (n=13,208)**	**Oral CEE-alone (n=16,508)**	**Oral Estradiol (n=3,024)**	**Transdermal Estradiol (n=2,187)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Treated	560 (26.5)	5948 (24.8)	873 (26.1)	2473 (19.0)	4880 (30.1)	604 (20.2)	447 (20.7)
High cholesterol requiring medication	306 (14.6)	3146 (13.2)	410 (12.3)	1439 (11.1)	2417 (14.9)	366 (12.3)	312 (14.5)
Hysterectomy	1106 (51.5)	12579 (51.6)	2744 (80.8)	0 (0)	16508 (100)	1661 (54.9)	1545 (70.6)
Oophorectomy							
None	1352 (64.2)	15631 (65.3)	1413 (42.8)	12539 (95.4)	5588 (35.0)	1893 (63.7)	1132 (52.4)
Partial	185 (8.8)	2001 (8.4)	359 (10.9)	541 (4.1)	1995 (12.5)	249 (8.4)	212 (9.8)
Bilateral	568 (27.0)	6304 (26.3)	1527 (46.3)	59 (0.4)	8384 (52.5)	831 (28.0)	816 (37.8)

CEE denotes conjugated equine estrogens.

*Low-dose CEE is defined as <0.625 mg/d. +Conventional-dose CEE is defined as 0.625 mg/d.

#High-dose CEE is defined as >0.625 mg

**included the formulations of both oral CEE and oral estradiol with a progestin or progesterone

Table 2

Direct Comparison of Transdermal HT and Oral Low-Dose CEE versus Conventional Dose CEE, updating HT use during follow-up

Outcome	Transdermal HT vs. Oral Conventional-dose CEE				Oral Low dose CEE vs. Oral Conventional-dose CEE			
	# cases by baseline HT		HR (95% CI)[1,2]		# cases by baseline HT		HR (95% CI)[1,2]	
	Transdermal	Conv. dose CEE			Low dose CEE	Conv. dose CEE		
Major CHD	18	324	0.63	(0.37, 1.06)	22	324	0.82	(0.57, 1.19)
Stroke	17	297	0.87	(0.55, 1.38)	36	297	1.07	(0.76, 1.49)
Total CVD	36	634	0.82	(0.59, 1.14)	59	634	0.86	(0.67, 1.12)
CVD Mortality	9	188	0.94	(0.50, 1.74)	19	188	0.87	(0.54, 1.42)
All-Cause Mortality	44	654	1.06	(0.78, 1.44)	65	654	0.98	(0.75, 1.28)

Major CHD = nonfatal MI and CHD mortality, Total CVD =major CHD, stroke and CVD mortality, Major CHD = nonfatal MI and CHD mortality, CEE denotes conjugated equine estrogens. Low-dose CEE is defined as <0.625 mg/d. Conventional-dose CEE is defined as 0.625 mg/d.

[1] All HR are from a Cox proportional hazard model stratified by baseline 5-year age intervals and history of CVD, and adjusted for age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), smoking (never, former, current), quartiles of total recreational physical activity, BMI categories (<25, 25-<30, ≥30), BMI (linear), hypertension (never, untreated, treated), treated diabetes (no,yes), high cholesterol requiring medication or current lipid lowering medication use (no,yes), hysterectomy (no,yes), oophorectomy (no, partial, bilateral), education and household income.

[2] Also adjusted for progestin or progesterone use.

Table 3

Direct Comparison of Oral Estradiol and Oral E+P versus Oral Conventional-Dose CEE, updating HT use during follow-up

Outcome	Oral Estradiol vs. Oral Conventional-dose CEE				Oral E+P vs. Oral Conventional-dose CEE alone			
	# cases by baseline HT		HR (95% CI)[1,2]		# cases by baseline HT		HR (95% CI)[1]	
	Estradiol	Conv. CEE			Oral E+P	Conv. CEE alone		
Major CHD	40	324	1.13	(0.79, 1.61)	138	258	1.02	(0.80, 1.31)
Stroke	21	297	0.64	(0.40, 1.02)	110	265	0.97	(0.75, 1.26)
Total CVD	65	634	0.93	(0.71, 1.23)	259	531	1.01	(0.85, 1.21)
CVD Mortality	23	188	1.33	(0.84, 2.12)	77	159	0.97	(0.69, 1.37)
All-Cause Mortality	81	654	1.09	(0.83, 1.43)	314	511	1.14	(0.95, 1.37)

Total CVD = total CHD, stroke and CVD mortality, Major CHD = nonfatal MI and CHD mortality, CEE denotes conjugated equine estrogens. Conventional-dose CEE is defined as 0.625 mg/d. Oral E+P is includes the formulations of both oral CEE and oral estradiol with a progestin or progesterone

[1] All HR are from a Cox proportional hazard model stratified by baseline 5-year age intervals and history of CVD, and adjusted for age (linear), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), smoking (never, former, current), quartiles of total recreational physical activity, BMI categories (<25, 25-<30, ≥30), BMI (linear), hypertension (never, untreated, treated), treated diabetes (no,yes), high cholesterol requiring medication or current lipid lowering medication use (no,yes), hysterectomy (no,yes), oophorectomy (no, partial, bilateral), education and household income.

[2] Also adjusted for progestin or progesterone use.