Timing and Duration of Menopausal Hormone Treatment May Affect Cardiovascular Outcomes

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Abstract

Largely on the basis of the first publication of findings of net harm with menopausal hormone treatment in the Women's Health Initiative (WHI) hormone trials, current Food and Drug Administration recommendations limit menopausal hormone treatment to the "… shortest duration consistent with treatment goals …," with goals generally taken to mean relief of menopausal symptoms and maximal duration as approximately 5 years. The WHI finding of net harm was due largely to the absence of beneficial effects on coronary heart disease incidence rates. Published analyses of WHI data by age or time since menopause find that excess coronary heart disease risk with menopausal hormone treatment is confined to more remotely menopausal or older women, with younger women showing nonsignificant trends toward benefit (the "timing hypothesis"). Moreover, a recently published reexamination of data from the WHI Estrogen plus Progestin trial suggests that reduced coronary heart disease risk may appear only after 5 to 6 years of treatment. Consistent with this finding, risk ratios for coronary heart disease were calculated as 1.08 (95% confidence interval, 0.86–1.36) in years 1 to 6 and as 0.46 (confidence interval, 0.28–0.78) in years 7 to 8+ in the WHI Estrogen Alone trial. Previous studies also support the beneficial effects of menopausal hormone treatment after prolonged exposure. Thus, current analyses do not support a generalized recommendation for short duration of menopausal hormone treatment. Rather, they

suggest that current Food and Drug Administration practice guidelines should be reconsidered to allow individualized care based on risk:benefit considerations. New research is urgently needed evaluating influences of timing, duration, dose, route of administration, and agents on menopausal hormone treatment-related risks and benefits to better understand how to optimize recommendations for individual patients.

Keywords

Cardiovascular disease; Estrogen; Hormones; Menopause; Women's health

Coronary heart disease remains the single greatest cause of death among women aged more than 50 years.[1] Before 2002, it was widely believed that menopausal hormone treatment protected women against coronary heart disease, according to the results of several large-scale observational studies showing 40% to 50% lower coronary heart disease incidence in women receiving menopausal hormone treatment.[2–9] In observational studies and randomized clinical trials, menopausal hormone treatment also has been found to significantly reduce the risks of osteoporosis-related fractures[10–12] and colon cancer,[13,14] while increasing breast cancer incidence by 20% to 30%.[15–17] On the basis of the expectation of coronary heart disease protection, the benefit/risk ratio for menopausal hormone treatment has been calculated to be positive for most women.[18] In 2002, primary results of the Women's Health Initiative (WHI) Estrogen plus Progestin (E+P) trial[14] showed the expected degrees of increase in breast cancer and thromboembolic disease without the expected coronary heart disease protection, leading to the conclusion that menopausal hormone treatment produces net harm. The results of the WHI Estrogen Alone (EA) trial, published in 2004,[19] showed a trend toward decreased risk of breast cancer, increased risks of stroke and venous thromboembolic disease, and again no coronary heart disease benefit. Publication of these findings led tens of millions of symptomatic women in the United States alone to discontinue menopausal hormone treatment or to avoid starting it. Thus, it is crucial to understand the reasons for the apparent discrepancies in coronary heart disease risk outcomes between observational studies and WHI trials.

WOMEN'S HEALTH INITIATIVE FINDINGS AND THE "TIMING HYPOTHESIS"

One difference between the WHI hormone trials and the observational studies is that women enrolled in the WHI were an average of 63 years of age at menopausal hormone treatment initiation, approximately 12 years postmenopausal on average.[14,19–21] In sharp contrast, enrollees in the observational studies tended to start menopausal hormone treatment at or near menopause, at an average age of 51 years.[22] Thus, women in the WHI also were older and longer postmenopausal than is usual for initiation of menopausal hormone treatment in clinical practice.[23] Because atherosclerotic lesions accumulate long before a first clinical event occurs,[24,25] the older women in the WHI trials may have harbored significant subclinical coronary heart disease, and thus would not have been good candidates for a treatment such as menopausal hormone treatment, which seems to be more effective in primary rather than secondary prevention of atherosclerosis. The idea that differences in age or time since menopause when menopausal hormone treatment is initiated may account for differences in coronary heart disease outcomes, and even opposite effects of menopausal hormone treatment on coronary heart disease have become known as the "timing hypothesis."[24,26–28]

Evidence for the timing hypothesis comes from varied sources. In an experimental model with surgically menopausal monkeys that develop typical atherosclerosis when fed a high saturated fat diet, estrogen treatment reduces coronary atherosclerosis by 50% to 70% if

begun immediately after ovariectomy.[29–31] In contrast, estrogen treatment has no beneficial effect when delayed by 2 years, which is the equivalent of approximately 6 years delay in humans. [32] This finding is consistent with the lack of secondary coronary heart disease prevention by menopausal hormone treatment observed in trials in women with a clinical history of heart disease.[33–35]

In the Nurses' Health Study, women initiating menopausal hormone treatment at or near menopause were observed to experience significant coronary heart disease protection (hazard ratio [HR] = 0.66, 95% confidence interval [CI], 0.54–0.80 for EA; HR = 0.72, 95% CI, 0.56–0.92 for E+P), whereas the few who started menopausal hormone treatment 10+ years after menopause were not (HR = 0.87, 95% CI, 0.69–1.10 for EA; HR = 0.90, 95% CI, 0.62–1.29 for E+P).[36]

Subgroup analyses of WHI data also support the timing hypothesis. For example, as shown in Figure 1A, in the E+P trial a nonsignificant trend toward protection (HR = 0.89; 95% zCI, 0.5–1.5) was seen in women who were less than 10 years post-menopausal, whereas significant excess risk occurred in women more than 20 years postmenopausal (HR = 1.71; 95% CI, 1.1–2.5).[20] Similarly, as shown in Figure 1B, in the EA trial[19,37] there was a trend for coronary heart disease protection in women 50 to 59 years of age (HR = 0.63; 95% CI, 0.36–1.08), but a trend toward increased risk in women aged more than 70 years (HR = 1.11; 95% CI, 0.82–1.52). Similar trends were seen when data from both E+P and EA trials were pooled.[38] Also, conjugated equine estrogen-treated women, who were 50 to 59 years old at randomization into the EA trial, showed a significantly lower mean coronary calcium burden compared with those treated with placebo when studied 8.7 (mean) years after randomization.[39]

Finally, a large meta-analysis of randomized clinical trials comparing coronary heart disease outcomes after menopausal hormone treatment started in younger versus older women reported reduced coronary heart disease only in the younger women.[40] In a complementary cost– benefit analysis, Salpeter et al[41] found that quality adjusted life-years for menopausal hormone treatment are immediately positive in younger women, but, apropos of the duration effects discussed next, shift from negative to positive only after a significant delay in older women.

In contrast with those findings, a recent post hoc analysis that pooled observational data from WHI participants who initiated menopausal hormone treatment on their own when recently menopausal (but whose duration of treatment was unknown) with data from women randomized to study drug within 5 years of menopause failed to detect a timing effect. [42] This finding may reflect the fact that duration of treatment was not considered in the analysis.

The "timing hypothesis" has been discussed widely and is included in the conclusions of a consensus scientific statement recently published by the Endocrine Society, which states in part that "Subgroup analyses suggest that the lack of benefit or increase in coronary heart disease risk observed in the overall analysis of the WHI resulted from harmful effects of menopausal hormone treatment in older women starting therapy many years after onset of menopause." [43] However, this hypothesis awaits rigorous testing. Two currently ongoing randomized clinical trials of menopausal hormone treatment address the timing hypothesis, the Kronos Early Estrogen Prevention Study,[44] which compares 2 hormone regimens (oral conjugated equine estrogen vs transdermal estradiol, both with cyclic oral progesterone) with placebo in women less than 3 years postmenopausal, and the Early Versus Late Intervention Trial With Estradiol (Howard Hodis, Principal Investigator), which examines effects of oral estradiol in recently and more remotely menopausal women. Both trials

monitor the development or progression of atherosclerosis as detected by noninvasive cardiovascular imaging. Neither is powered for clinical event outcomes.

EFFECTS OF TREATMENT DURATION IN THE WOMEN'S HEALTH INITIATIVE ESTROGEN + PROGESTIN TRIAL

A second important issue, also apparently critical in the relationship between menopausal hormone treatment and atherosclerosis but less widely discussed to date, is that of treatment duration, that is, whether early and late menopausal hormone treatment effects on coronary heart disease risk may differ. The WHI findings led directly to a revised Food and Drug Administration "black box" warning for estrogens intended for menopausal hormone treatment, stating in part that "Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman."[45] In practice, the "shortest duration" for menopausal hormone treatment is usually interpreted as no more than 5 years to reduce the risk for breast cancer, which may increase after 5 years of treatment.[17] Ironically, observational studies addressing the issue of menopausal hormone treatment duration indicate that protective effects of menopausal hormone treatment against coronary heart disease may become apparent only after several years of treatment.[46,47] This finding is supported by a recent post hoc analysis of data from the WHI E+P trial[48] showing that, in adherent women initiating treatment at less than 10 years of menopause, the coronary heart disease event-free survival rate was slightly lower in the menopausal hormone treatment group than in the placebo group during the first 5 years of treatment, but at 6 years the placebo and treatment group curves crossed one another showing a nonsignificant, late trend toward greater event-free survival in the menopausal hormone treatment group ($P = .44$ for differences between these 2 survival curves). The survival curves for women of all ages and for women initiating treatment 10 or more years after menopause indicated a small advantage for the placebo-treated women at all time points, with P values of .057 and .011, respectively, consistent with the timing hypothesis. For continuous treatment of women initiating menopausal hormone treatment at less than 10 years since menopause, there were nonsignificant HRs indicating an increased risk for the first 2 years (HR = 1.29; 95% CI, 0.52–3.18), a decreased risk after 2 years (HR = 0.63; 95% CI, 0.27–1.52), and an overall 8-year decrease in risk (HR = 0.64; 95% CI, 0.21–1.99), the latter also nonsignificant. However, the difference between the ≤2-year and the > 2-year HRs was statistically significant ($P = .038$), suggesting a duration effect. The authors did not compare HRs for ≤5 years and > 5 years in all likelihood because so few women in the WHI E+P trial were treated beyond 5 years because the trial was stopped early for harm, seen primarily in the older women.

EFFECTS OF TREATMENT DURATION IN THE WOMEN'S HEALTH INITIATIVE ESTROGEN ALONE TRIAL

To investigate whether menopausal hormone treatment with EA might show a similar reduction in coronary heart disease risk with longer duration of use, as suggested by analyses of the E+P data, we evaluated published results of the WHI EA trial, which was continued for approximately 2 years longer than the E+P trial.[19] On the basis of the findings of Toh et al[48] in the WHI E+P study that survival curves crossed in the more recently menopausal women at 6 years, annual coronary heart disease event incidence rates for years 1 to 8+ and rate ratios and 95% CIs for coronary heart disease incidence rates pooled across 2 periods (years 1–6 and >6 years) were calculated using a Poisson model,[49] accounting for person-years at risk in both groups. We approximated the person-years by summing the number of participants within the placebo and conjugated equine estrogen groups contributing follow-up during each of the years in the first and second pooled time periods.

The absolute numbers of coronary heart disease events and women at risk in the conjugated equine estrogen-treated and placebo-treated groups in each year of the WHI EA trial[19] are shown in Table 1. The annual coronary heart disease event incidence rates appeared similar in conjugated equine estrogen- and placebo-treated women in years 1 to 6, but declined sharply in the conjugated equine estrogen-treated women thereafter (Figure 2). As shown in Table 2, the rate ratios for years 1 to 6 and 7 to 8+ identify a statistically significant ($P = .003$) reduction in coronary heart disease risk with more than 6 years of use of conjugated equine estrogen compared with placebo.

INTERPRETATION AND PERSPECTIVE

Our post hoc analysis of the WHI EA trial results corroborates recent findings in the E+P trial,[48] demonstrating a trend for decrease in cardiovascular risk after 6 years of menopausal hormone treatment. The significantly reduced rate ratio after 6 years is particularly striking because it is not confined to the younger or more recently menopausal women, as was true for the E+P analysis[48] but was calculated using data from all women enrolled in the WHI EA trial (ages 50–79 years). The finding of cardiovascular protection with treatment more than 6 years also is consistent with findings in the Nurses' Health Study[46,50] and a trend seen in older women with preexisting coronary heart disease in the Heart and Estrogen/ Progestin Replacement Study.[33] Furthermore, in a case-control study of women with an acute myocardial infarction versus age-matched community controls,[47] menopausal hormone treatment was associated with a significant reduction in the likelihood for an acute myocardial infarction (HR = 0.42; 95% CI, 0.24–0.73) only when used for more than 60 months. Consistent with those findings, in postmenopausal women undergoing coronary angiography, strong inverse relationships were observed between years of menopausal hormone treatment exposure and both the degree of stenosis and the severity score.[51]

Although the timing of initiation of menopausal hormone treatment in relation to menopause onset has been a matter of debate, there has been little discourse and no working hypothesis regarding the likely effect of duration of menopausal hormone treatment on coronary heart disease risk. Because atherogenesis is a gradual process, progressing from fatty streaks to advanced plaques over a number of years, an intervention whose beneficial effects are confined to halting or slowing progression would not be expected to show benefit until sufficient time had elapsed to reduce the number of at-risk plaques. Menopausal hormone treatment reduces low-density lipoprotein cholesterol and lipoprotein(a), and increases high-density lipoprotein cholesterol,[52–56] lowers fibrinogen levels,[52] improves responsiveness of the arterial endothelium to vasodilatory stimuli,[54,57] decreases expression of certain endothelial adhesion factors,[58–60] reduces blood pressure,[61–63] and acts as an antioxidant.[64–68] All of these actions would be expected to inhibit initiation of atherosclerosis and slow progression of early atherosclerotic lesions.

On the other hand, oral estrogens also can have adverse effects that are more rapidly manifest and that may help explain the observed trends for early increase in coronary heart disease risk in older or more remotely menopausal women, as observed in the WHI trials.[14,19–21] Increases in thrombotic and decreases in thrombolytic factor syntheses by the liver induced by the first-pass effects of high concentrations of oral estrogen in the portal circulation[69–74] may explain the 2- to 3-fold increase in risk of venous thromboembolic disease observed with oral but not transdermal estrogen,[75,76] and could contribute to the risk of coronary thrombosis on existing plaque. Also, estrogens induce macrophage and vascular smooth muscle expression of matrix metalloproteinase in the fibrous caps of existing plaque,[77–80] which may lead to plaque rupture and consequent vascular occlusion. These latter effects would tend to heighten the short-term risk of a coronary heart disease event in women with preexisting advanced plaques.

A potential weakness of our analysis is that the apparent late-onset coronary heart disease protection occurring in the WHI and other studies could be a "healthy survivor effect." This might have occurred if estrogen-treated women at high risk because of the presence of advanced plaque had an increased incidence of early coronary heart disease events, thus, removing them from the study and leaving a residual group with better cardiovascular health for later follow-up. This explanation seems unlikely because during the first 6 years of the EA trial there was an excess of only 9 events (3.9/10,000 woman years) in the conjugated equine estrogen group, whereas in years 6 to 8+ there was an excess of 31 events (36.6/10,000 woman years) in the placebo group (Table 2). That said, it remains the case that our analysis of the WHI EA data could have been improved by access to original patient-level data allowing adjustment for compliance and other factors as carried out by Toh et al[48] for the E+P study.

Both published clinical observations and considerations of mechanisms of estrogen actions influencing the pathogenesis of coronary heart disease make a plausible case that biphasic effects of menopausal hormone treatment on coronary heart disease risk depend on both timing of initiation and duration of treatment. The present analysis of the WHI EA trial, taken together with a recent analysis of E+P trial data,[48] suggests that the longer the duration of menopausal hormone treatment, the more favorable the effects on coronary heart disease risk. Thus, treatment duration and timing of menopausal hormone treatment initiation seem to be distinct factors that may help explain the disparity in coronary heart disease outcomes between the observational studies and the WHI randomized clinical trials. Because younger, recently menopausal women have a relatively low prevalence of at-risk plaque and a correspondingly low incidence of coronary heart disease events, the "early harm" effect is likely to be clinically insignificant in this population. However, coronary heart disease risk in women increases steeply from age 55 to 70 years, just the time at which long-term menopausal hormone treatment initiated at menopause seems to confer coronary heart disease protection.

CONCLUSIONS

The current analysis and data reviewed do not support any specific limit on the duration of menopausal hormone treatment. Emerging data suggest that the decision to prescribe menopausal hormone treatment and how long to continue should be flexible, based on patient characteristics (eg, age and time since menopause) and the balance of benefits (symptom relief, coronary heart disease, and bone fractures) and risks (breast cancer, thromboembolic disease, and stroke). We believe that guidelines from the Food and Drug Administration and other official sources should be reconsidered and revised to reflect this personalized approach to the patient.[81] New research is urgently needed to further evaluate influences of timing, duration, dose, route of administration, and choice of agents on menopausal hormone treatment risks and benefits to optimize recommendations for individual patients.

Acknowledgments

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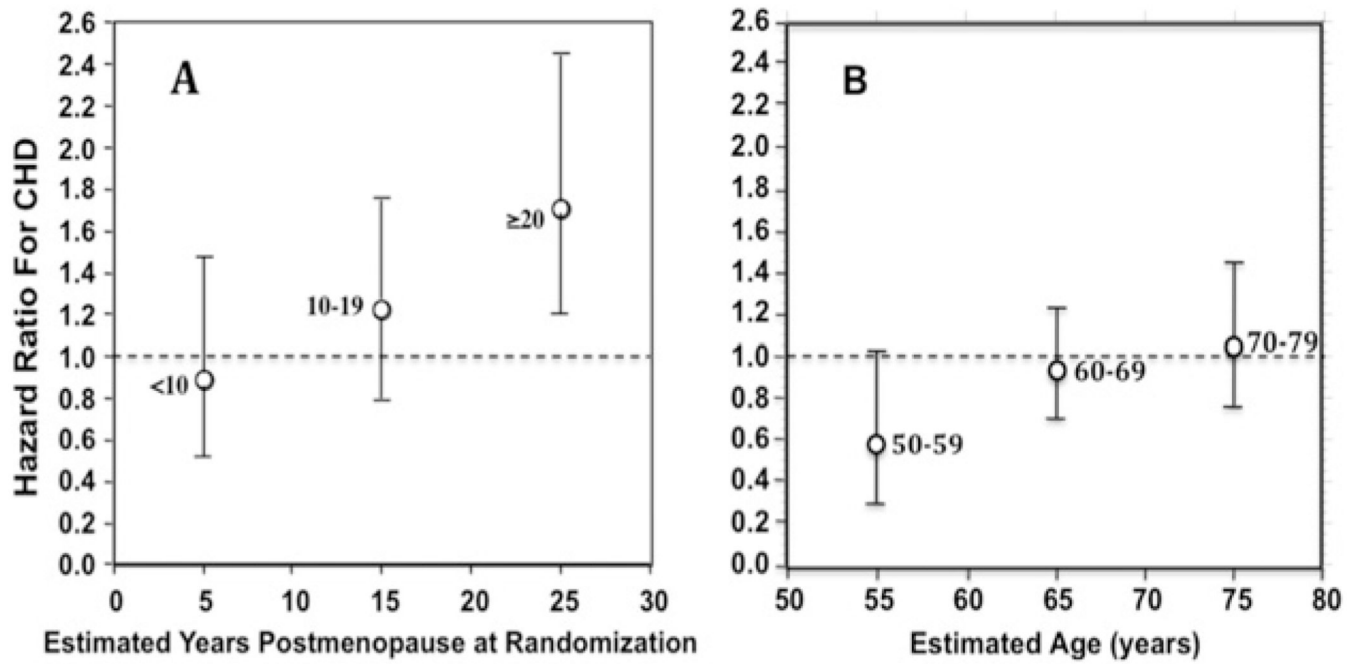
Figure 1.
HRs and 95% CIs for coronary heart disease in WHI hormone trials. **A,** By time since menopause in the E+P study (redrawn from Manson et al[20]). **B,** By age group in EA study (redrawn from Anderson et al[19] and Hsia et al[37]). CHD = coronary heart disease.
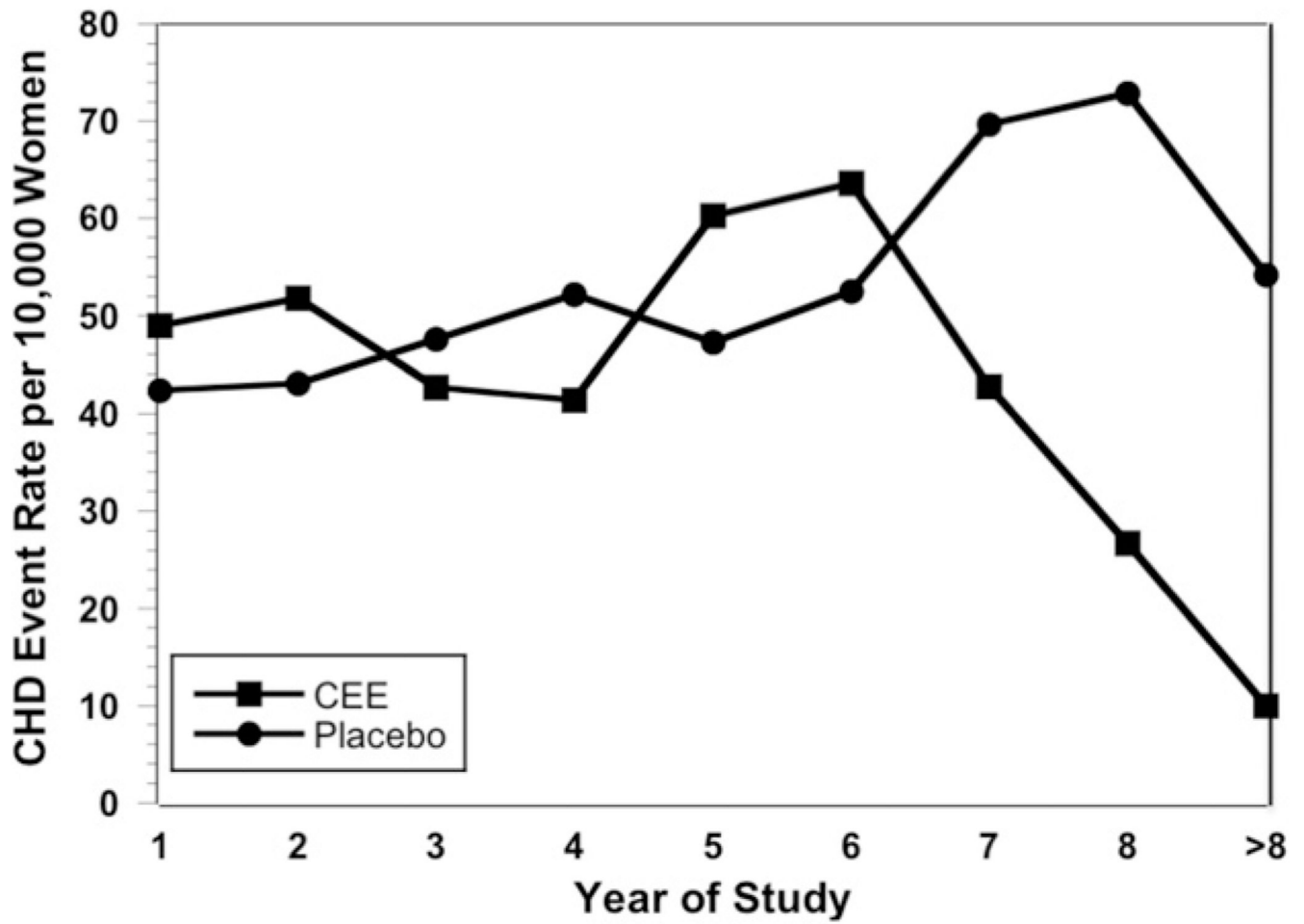
Figure 2.
Annual incidence of coronary heart disease events per 10,000 women in the WHI EA trial.
Data from Anderson et al[19] and Hsia et al.[37] CEE = conjugated equine estrogen; CHD =
coronary heart disease.

Table 1

Numbers of Coronary Heart Disease Events and Women at Risk in Each Year of Women's Health Initiative Estrogen Alone Trial

	Year	1	2	3	4	5	6	7	8	>8
Conjugated equine estrogen	Events	26	27	22	21	30	31	13	6	1
	At risk	5310	5210	5147	5067	4978	4874	3034	2248	999
Placebo	Events	23	23	25	27	24	26	28	17	6
	At risk	5429	5336	5254	5171	5072	4950	4015	2331	1106

Table 2

Event Numbers and Rate Ratios for Coronary Heart Disease Events in Early and Late Periods of the Women's Health Initiative Estrogen Alone Trial

Years	Numbers	Conjugated Equine Estrogen	Placebo	Rate Ratio	Standard Error	95% Confidence Interval
1–6	Events	157	148	1.08	0.124	0.86–1.36
	At risk	30,586	31,212			
7–8+	Events	20	51	0.46	0.123	0.28–0.78
	At risk	6281	7452			