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Estrogen plus Progestin and the Risk of Coronary Heart Disease

JoAnn E. Manson, M.D., Dr.P.H., Judith Hsia, M.D., Karen C. Johnson, M.D., M.P.H., Jacques E. Rossouw, M.D., Annlouise R. Assaf, Ph.D., Norman L. Lasser, M.D., Ph.D., Maurizio Trevisan, M.D., Henry R. Black, M.D., Susan R. Heckbert, M.D., Ph.D., Robert Detrano, M.D., Ph.D., Ora L. Strickland, Ph.D., Nathan D. Wong, Ph.D., John R. Crouse, M.D., Evan Stein, M.D., and Mary Cushman, M.D., for the Women's Health Initiative Investigators*

ABSTRACT

BACKGROUND

Recent randomized clinical trials have suggested that estrogen plus progestin does not confer cardiac protection and may increase the risk of coronary heart disease (CHD). In this report, we provide the final results with regard to estrogen plus progestin and CHD from the Women's Health Initiative (WHI).

METHODS

The WHI included a randomized primary-prevention trial of estrogen plus progestin in 16,608 postmenopausal women who were 50 to 79 years of age at base line. Participants were randomly assigned to receive conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo. The primary efficacy outcome of the trial was CHD (nonfatal myocardial infarction or death due to CHD).

RESULTS

After a mean follow-up of 5.2 years (planned duration, 8.5 years), the data and safety monitoring board recommended terminating the estrogen-plus-progestin trial because the overall risks exceeded the benefits. Combined hormone therapy was associated with a hazard ratio for CHD of 1.24 (nominal 95 percent confidence interval, 1.00 to 1.54; 95 percent confidence interval after adjustment for sequential monitoring, 0.97 to 1.60). The elevation in risk was most apparent at one year (hazard ratio, 1.81 [95 percent confidence interval, 1.09 to 3.01]). Although higher base-line levels of low-density lipoprotein cholesterol were associated with an excess risk of CHD among women who received hormone therapy, higher base-line levels of C-reactive protein, other biomarkers, and other clinical characteristics did not significantly modify the treatment-related risk of CHD.

CONCLUSIONS

Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease.

From the Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (J.E.M.); the Department of Medicine, George Washington University, Washington, D.C. (J.H.); the Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis (K.C.J.); the Program Office, National Heart, Lung, and Blood Institute, Bethesda, Md. (J.E.R.); Memorial Hospital, Brown Medical School, Pawtucket, R.I. (A.R.A.); the Preventive Cardiology Program, New Jersey Medical School, Newark (N.L.L.); the Department of Social and Preventive Medicine, University at Buffalo, Buffalo, N.Y. (M.T.); the Department of Preventive Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago (H.R.B.); the Department of Epidemiology, University of Washington, Seattle (S.R.H.); the Division of Cardiology, Harbor-UCLA Research and Education Institute, Torrance, Calif. (R.D.); the Woodruff School of Nursing, Emory University, Atlanta (O.L.S.); the Heart Disease Prevention Program, University of California, Irvine (N.D.W.); the Department of Medicine, Wake Forest University, Winston-Salem, N.C. (J.R.C.); Medical Research Laboratories International, Highland Heights, Ky. (E.S.); and the Departments of Medicine and Pathology, University of Vermont, Burlington (M.C.). Address reprint requests to Dr. Manson at the Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave., Boston, MA 02215, or at jmanson@rics.bwh.harvard.edu.

*The Women's Health Initiative (WHI) investigators are listed in the Appendix.

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OUR UNDERSTANDING OF THE EFFECT of postmenopausal hormone therapy on the risk of coronary heart disease (CHD) has recently undergone a major change. Although previous observational studies had suggested that postmenopausal hormone therapy was associated with a reduction of 40 to 50 percent in the risk of CHD,^{1,2} recent randomized clinical trials have provided no evidence of cardiac protection and even some evidence of harm with postmenopausal hormone therapy.³⁻⁸ The primary findings of the Estrogen plus Progestin trial of the Women's Health Initiative (WHI) suggested an overall increase in the risk of CHD (hazard ratio, 1.29) among women randomly assigned to combined hormone therapy as compared with those assigned to placebo.⁸ The trial was stopped early, after an average of 5.2 years of follow-up, because it was found that the health risks associated with estrogen plus progestin exceeded the benefits.

It has been hypothesized that divergent findings from observational studies and randomized clinical trials may be at least partially attributable to differences in the clinical characteristics of the study populations, including differences in age, years since menopause, and underlying risk of CHD, as well as methodologic limitations of observational studies.^{9,10} Moreover, certain biomarkers, including base-line levels of lipoproteins, inflammatory markers, and thrombotic factors, may identify women for whom postmenopausal hormone therapy confers a higher or lower risk of coronary events.¹¹⁻¹⁴

In this article, we present the final results of the WHI trial of the relation between the use of estrogen plus progestin and the risk of CHD. We provide an updated analysis of coronary end points reached through the termination of the trial on July 7, 2002 (previous analyses included end points reached through April 2002). We use centrally adjudicated end points for the primary coronary outcome of nonfatal myocardial infarction or death due to CHD (previous analyses were based on local adjudication) to enhance the uniformity of documentation of outcomes. We also provide results for additional coronary end points, including angina, acute coronary syndromes, and congestive heart failure, and provide detailed analyses of subgroups of women defined according to clinical characteristics and biomarker levels to further elucidate the primary findings.

METHODS

STUDY POPULATION, RECRUITMENT, STUDY REGIMENS, AND FOLLOW-UP

Detailed information about the study population, recruitment methods, study regimens, randomization, blinding, follow-up, data and safety monitoring, and quality assurance has been published previously.^{8,15} Briefly, eligible women were 50 to 79 years of age at the time of initial screening, were postmenopausal, and were likely to be residing in the same geographic area for at least three years.

Postmenopausal women with an intact uterus at screening were eligible for the trial of combined estrogen and progestin; women who had undergone hysterectomy were eligible for the trial of estrogen alone. The protocol and consent forms were approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all participants. The sample analyzed here consists of the 16,608 women with an intact uterus at base line who were enrolled in the double-blind trial comparing estrogen plus progestin with placebo. The study regimen of combined estrogen and progestin was provided in one daily tablet containing 0.625 mg of oral conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate (Prempro, Wyeth). The control group received matching placebo.

ASCERTAINMENT OF OUTCOMES

CHD was defined as acute myocardial infarction necessitating overnight hospitalization, death due to CHD, or silent myocardial infarction identified on serial electrocardiography.¹⁶ The diagnosis of acute myocardial infarction was documented by a review of the medical records according to an algorithm that was adapted from standardized criteria,^{8,17} including cardiac pain, cardiac enzyme and troponin levels, and electrocardiographic readings. Death due to CHD was defined as death consistent with an underlying cause of CHD plus one or more of the following factors: hospitalization for myocardial infarction within 28 days before death, previous angina or myocardial infarction, death due to a procedure related to CHD, or a death certificate consistent with an underlying cause of CHD. Silent myocardial infarction¹⁶ was diagnosed through the comparison of base-line and follow-up electrocardiograms at three and six years. Additional coronary end points included coronary revascularization (coronary-artery bypass grafting [CABG] or

percutaneous transluminal coronary angioplasty [PTCA]) confirmed by a review of the medical records, angina necessitating hospitalization (hospital admission for chest pain or other symptoms determined to be due to angina), confirmed angina (hospitalization for angina, with myocardial ischemia confirmed by stress testing or obstructive coronary disease [luminal narrowing of >70 percent] confirmed by coronary angiography), acute coronary syndromes (hospitalization for angina, Q-wave infarction, or non-Q-wave infarction), and congestive heart failure (necessitating hospitalization, with a physician's diagnosis of congestive heart failure and pertinent abnormalities on diagnostic testing corroborated by a review of the medical records). Acute myocardial infarctions and deaths due to CHD were confirmed by central physician-adjudicators and other coronary end points by local adjudicators, all of whom were unaware of the treatment-group assignments. The rate of concordance between the local and central reviews was 90 percent for myocardial infarction and 97 percent for death due to atherosclerotic CHD.

ANALYSES OF BIOMARKERS

Blood was drawn at base line after a fast lasting a minimum of 10 hours. Serum and plasma samples were shipped to a central repository and stored at -70°C .¹⁸ In a random sample of 8.6 percent of participants (oversampled for women from minority groups), the lipid profile was obtained and glucose and insulin were measured at base line, year 1, and year 3. The assay methods have been described previously.¹⁸

A nested case-control study of biomarkers, treatment-group assignment, and risk of CHD was also conducted. A total of 205 cases of myocardial infarction or death due to CHD occurring between randomization and February 28, 2001, were included. Controls were selected from the hormone-therapy trial and were matched to the cases according to age, date of randomization, presence or absence of CHD at base line, hysterectomy status, and follow-up time. Additional controls selected for cases of stroke or venous thrombosis were also included; the total number of controls was 513. Methods of testing for the inflammatory and thrombotic markers have been described previously.¹⁸ Data analysis was performed with the use of logistic regression.

STATISTICAL ANALYSIS

Primary analyses used time-to-event methods based on the intention-to-treat principle. For coronary

outcomes, the time to the event was defined as the number of days between randomization and the first diagnosis after randomization. Comparisons with regard to the primary outcome are presented as hazard ratios with 95 percent confidence intervals that were calculated from Cox proportional-hazards analyses,¹⁹ stratified according to age, presence or absence of CHD at base line, and randomization status in the low-fat-diet trial (as in the original report⁸), and adjusted for the presence or absence of previous CABG or PTCA. Because CHD was the primary outcome of the hormone trial and was an important consideration for stopping the trial early⁸ (the trial was terminated after the 10th semiannual interim analysis), both nominal 95 percent confidence intervals and 95 percent confidence intervals adjusted for sequential monitoring are provided for the primary coronary end point. For other coronary end points, both nominal confidence intervals and confidence intervals adjusted for multiple (seven) trial outcomes are presented. Secondary analyses included women who adhered fully to the study medication.

Cox models for subgroup analyses were stratified according to age and the presence or absence of CHD at base line, and the consistency of treatment effects among subgroups was assessed by formal tests of interaction. Because of the large number of subgroups considered (at least 36), the results should be interpreted with caution, since some significant findings (at least one or two, based on a 0.05 nominal level of statistical significance) could have occurred by chance alone. All reported P values are two-sided.

RESULTS

BASE-LINE CHARACTERISTICS

As described in the original report,⁸ the base-line characteristics were nearly identical in the two treatment groups. The only base-line variable that differed significantly between the groups was a history of coronary revascularization (present in 1.1 percent of the women in the hormone group and 1.5 percent of those in the placebo group, $P=0.04$), so this variable was included as a covariate in the Cox models. A total of 8506 women were randomly assigned to estrogen plus progestin, and 8102 were assigned to placebo. The mean (\pm SD) age was 63.3 ± 7.1 years; 16 percent of the women were members of minority groups; and one quarter of the women had previously used postmenopausal hormone therapy. Approximately 2.4 percent of the women reported

previous CHD (myocardial infarction, a coronary revascularization procedure, or both) and 4.4 percent reported previous CHD, stroke, or transient cerebral ischemia. Thus, the prevalence of previous cardiovascular disease was low, and women with such a history were analyzed separately in secondary analyses. The base-line levels of cardiovascular risk factors (36 percent of the women had hypertension, 13 percent were being treated for hypercholesterolemia, 4.4 percent were being treated for diabetes, and 10.5 percent were current smokers) were consistent with those in a generally healthy population of postmenopausal women.

FOLLOW-UP AND ADHERENCE

Vital status was known for 16,067 women who underwent randomization (96.7 percent), including 485 (2.9 percent) who were known to be deceased. Information on outcomes was up to date for 15,582 women (93.8 percent); for the 541 women (3.3 percent) who were lost to follow-up or who stopped providing information on outcomes before the trial ended, we include all available information. The present report updates information on outcomes

through July 7, 2002 (after an average of 5.6 years of follow-up [as compared with 5.2 years in the earlier report⁸] and a maximum of 8.6 years). As previously reported,⁸ 42 percent of women randomly assigned to estrogen plus progestin and 38 percent of women randomly assigned to placebo stopped taking the study drugs during follow-up — rates that compare favorably with community-based adherence to hormone therapy.²⁰ The cumulative “drop-in” rate — the rate of hormone use initiated by the woman’s clinician — was 6.2 percent in the estrogen-plus-progestin group and 10.7 percent in the placebo group by year 6.

INTERMEDIATE BIOMARKERS AND RISK FACTORS FOR CHD

The results of assessments of CHD biomarkers, including fasting blood lipid, glucose, and insulin levels, in an 8.6 percent subsample of women at base line and at year 1 are shown in Figure 1. Women randomly assigned to estrogen plus progestin had greater reductions in the total cholesterol, low-density lipoprotein (LDL) cholesterol, glucose, and insulin levels and greater increases in the high-density

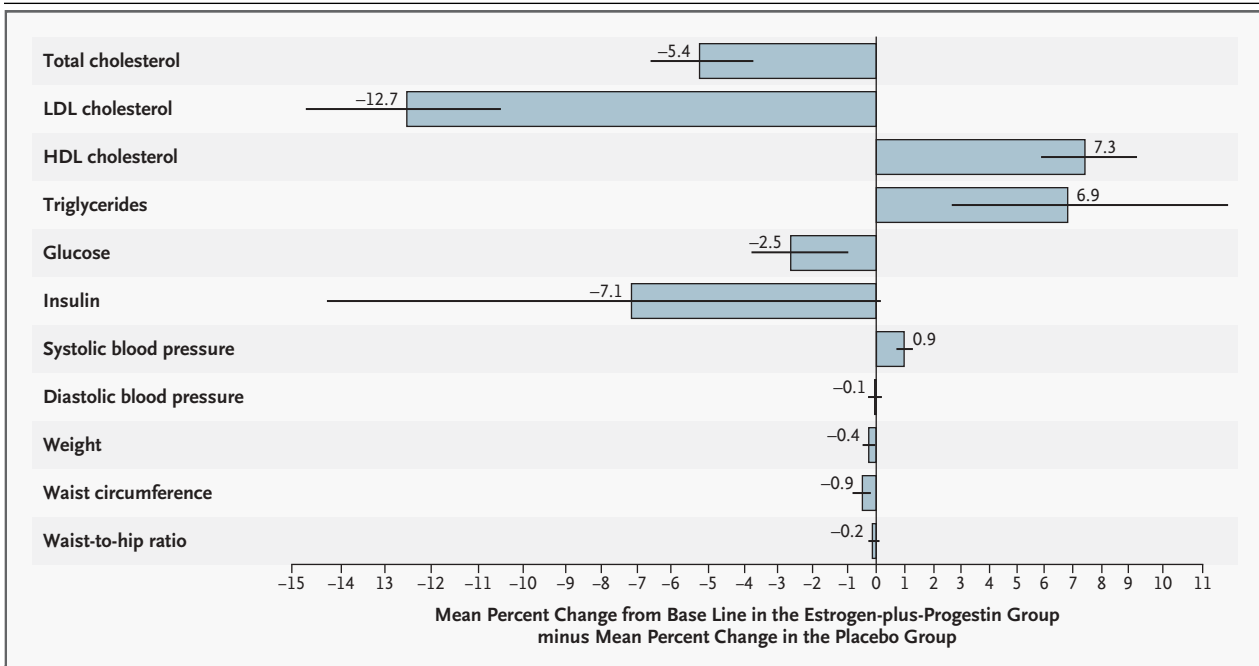


Figure 1. Differences between the Mean Percent Changes from Base Line to Year 1 in Several Intermediate Outcomes in the Estrogen-plus-Progestin Group as Compared with the Placebo Group. Horizontal lines represent the 95 percent confidence intervals. The differences between the groups were significant ($P < 0.05$) for total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, systolic blood pressure, weight, and waist circumference.

lipoprotein (HDL) cholesterol and triglyceride levels than women in the placebo group. Systolic blood pressure at year 1 was 1 mm Hg higher among women receiving hormones than among those receiving placebo (remaining 1 to 2 mm Hg higher during follow-up), although diastolic blood pressure did not differ materially between groups. Body weight and waist circumference at follow-up were slightly lower among women in the hormone group than among those in the placebo group, although the ratio of the waist circumference to the hip circumference did not differ appreciably (Fig. 1). Results at year 3 (data not shown) were nearly identical to those at year 1.

CLINICAL CORONARY OUTCOMES

Table 1 shows the rates of CHD (nonfatal myocardial infarction, including silent myocardial infarction, and death due to CHD), coronary revascular-

ization, angina, and congestive heart failure. In adjusted analyses, women randomly assigned to estrogen plus progestin had a risk of CHD that was 24 percent higher than that among women randomly assigned to placebo (hazard ratio, 1.24 [nominal 95 percent confidence interval, 1.00 to 1.54; 95 percent confidence interval with adjustment for sequential monitoring, 0.97 to 1.60]). The hazard ratios were 1.28 for nonfatal myocardial infarction and 1.10 for death due to CHD (total cases of CHD, 335, as compared with 286 in the earlier report⁸). Absolute rates of CHD were 39 cases per 10,000 person-years and 33 cases per 10,000 person-years for hormone therapy and placebo, respectively. No significant differences were observed with regard to coronary revascularization, hospitalization for angina, confirmed angina, acute coronary syndrome, or congestive heart failure.

Additional analyses were conducted to examine

Table 1. Coronary Outcomes among Women Randomly Assigned to Estrogen plus Progestin, as Compared with Those Assigned to Placebo.*

Variable	Estrogen-plus-Progestin Group (N=8506)	Placebo Group (N=8102)	Adjusted Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
Mean follow-up time (mo)	67.8	66.8			
	<i>no. of cases (annualized percentage)</i>				
CHD	188 (0.39)	147 (0.33)	1.24	1.00–1.54	0.97–1.60
Nonfatal MI					
Including silent MI	151 (0.31)	114 (0.25)	1.28	1.00–1.63	0.96–1.70
Excluding silent MI	147 (0.31)	109 (0.24)	1.30	1.01–1.67	0.97–1.74
Death due to CHD	39 (0.08)	34 (0.08)	1.10	0.70–1.75	0.65–1.89
CHD, revascularization, or angina	369 (0.77)	356 (0.79)	1.00	0.86–1.15	0.82–1.22
CABG or PTCA	214 (0.45)	205 (0.45)	1.01	0.83–1.22	0.77–1.31
Hospitalization for angina	172 (0.36)	195 (0.43)	0.86	0.70–1.05	0.65–1.13
Confirmed angina	106 (0.22)	126 (0.28)	0.82	0.63–1.06	0.57–1.17
Acute coronary syndrome	322 (0.67)	299 (0.66)	1.03	0.88–1.21	0.83–1.28
Congestive heart failure	113 (0.23)	109 (0.24)	0.99	0.76–1.29	0.69–1.42

* CHD includes acute myocardial infarction (MI) necessitating hospitalization, silent myocardial infarction as determined by serial electrocardiography, and death due to CHD. Hazard ratios and nominal 95 percent confidence intervals (CIs) are stratified according to age, presence or absence of a previous coronary event, and randomly assigned diet-modification group and are adjusted for the presence or absence of previous coronary-artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). The adjusted 95 percent confidence interval includes control for the above variables and further control for sequential monitoring (for the primary coronary end points) and for multiple (seven) trial outcomes (for the secondary coronary end points). Confirmed angina includes hospitalization for angina with myocardial ischemia confirmed by stress testing or obstructive coronary disease (luminal narrowing of >70 percent) confirmed by coronary angiography. Acute coronary syndromes include Q-wave myocardial infarction, non-Q-wave myocardial infarction, and hospitalization for angina. The numbers of events do not add up to the totals for the categories because some women had more than one event.

the sensitivity of these results to the actual use of study medications. Because a substantial proportion of women stopped taking study pills during follow-up, analyses were performed that censored the data on a woman's history of coronary events six months after she stopped taking the pills (or began taking less than 80 percent of them) or six months after she began nonstudy hormone therapy. These analyses produced higher estimates of the excess risk with estrogen plus progestin. For CHD, the adjusted hazard ratio was 1.50 (95 percent confidence interval, 1.14 to 1.97), and for CHD, revascularization, or angina, the hazard ratio was 1.09 (95 percent confidence interval, 0.90 to 1.31). If discontinuation of treatment and initiation of nonstudy hormone therapy occurred independently of the risk of CHD, it would suggest that the intention-to-treat analyses may underestimate the effect. Such "adherence-based" analyses, however, have limitations and should be interpreted with caution.

TEMPORAL TRENDS

The cumulative hazard rates of CHD (nonfatal myocardial infarction or death due to CHD) in the two treatment groups are provided in Figure 2. An elevated risk of CHD with estrogen plus progestin appeared to emerge soon after randomization, and the cumulative rates did not begin to converge until year 6.

Hazard ratios for CHD for one-year intervals of follow-up are presented in Table 2. A substantial elevation in the risk of CHD with estrogen plus progestin occurred in year 1 (hazard ratio, 1.81 [95 percent confidence interval, 1.09 to 3.01]), and a smaller and nonsignificant excess risk occurred in years 2 through 5. In year 6 and beyond, the increased rates in the placebo group resulted in an apparent risk reduction. The trend toward a decreasing relative risk over time was statistically significant. For CHD, revascularization, or angina, the hazard ratio was 1.48 (95 percent confidence interval, 1.03 to 2.11) at one year, but no elevation in the risk was apparent in subsequent years.

SUBGROUP ANALYSES

To determine whether certain subgroups of women were at particularly high or low risk for CHD (nonfatal myocardial infarction or death due to CHD) with estrogen plus progestin, we examined several demographic and clinical characteristics. In addition, base-line levels of several lipid, inflammatory, and thrombotic biomarkers were assessed as potential modulators of risk. Overall, no subgroup of women except those with higher base-line LDL cholesterol levels had evidence of a pattern of hazard ratios for CHD with postmenopausal hormone therapy that was different from the pattern found among all women. Subgroup analyses were planned a priori; the results of analyses of variables whose influence has greater biologic plausibility are shown in Figures 3 and 4, and the remainder are summarized in Table 3 or below.

Results of evaluations of the roles of age and the time since menopause in modulating the risk of treatment are shown in Figure 3. No significant interaction between age and treatment was observed. For women in whom menopause had begun less than 10 years previously, 10 to 19 years previously, and 20 or more years previously, the hazard ratios for CHD associated with postmenopausal hormone therapy were 0.89, 1.22, and 1.71, respectively, but the interaction was nonsignificant. Moreover, the

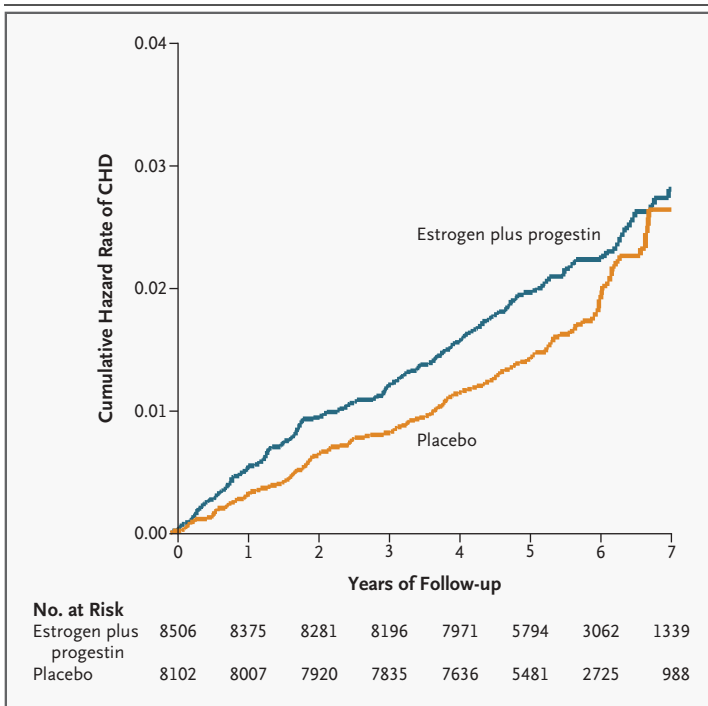


Figure 2. Kaplan–Meier Estimates of Cumulative Hazard Rates of CHD. CHD included nonfatal myocardial infarction and death due to CHD. The overall hazard ratio for CHD was 1.24 (nominal 95 percent confidence interval, 1.00 to 1.54; 95 percent confidence interval with adjustment for sequential monitoring, 0.97 to 1.60).

presence or absence of vasomotor symptoms (hot flashes, night sweats, or both) was not significantly related to the risk of CHD associated with postmenopausal hormone therapy, either among women 50 to 59 years of age (Fig. 3) or in the total cohort (hazard ratios, 1.26 and 1.25, respectively). Previous use of hormone therapy did not appreciably or consistently modify risk, regardless of the duration or temporal proximity of this use. Body-mass index (the weight in kilograms divided by the square of the height in meters) and other anthropometric measures (the waist circumference and the waist-to-hip ratio) did not clearly modulate the risk associated with postmenopausal hormone therapy, nor did the use of aspirin (≥ 80 mg per day) or statin therapy (Fig. 3).

The hazard ratios for CHD with estrogen plus progestin did not differ substantially according to ethnic group, level of education, or CHD-risk-factor status (Table 3) or according to the past use or nonuse of oral contraceptives or levels of physical activity (data not shown). Women who were current smokers or who had a history of hypertension or diabetes, a higher number of risk factors for CHD, or preexisting CHD or other cardiovascular disease did not have a significantly greater excess risk of subsequent coronary events with postmenopausal hormone therapy than did women without these risk factors (Table 3).

Women with higher base-line LDL cholesterol levels appeared to have a greater excess risk of CHD with hormone therapy (P for interaction=0.01, after adjustment for age, year of randomization, previous CHD, and use of statins at base line) (Fig. 4), but this finding may have been due to chance, given the large number of comparisons tested. No other subgroup defined according to biomarker levels, including the C-reactive protein level, had a risk of CHD with postmenopausal hormone therapy that differed significantly from the risk among all women (Fig. 4).

DISCUSSION

Our findings in predominantly healthy postmenopausal women 50 to 79 years of age document that combined estrogen and progestin does not confer cardiac protection and may slightly increase the risk of coronary events. These findings extend the information that has been published previously⁸ by including updated and centrally adjudicated primary

coronary end points, providing results for additional coronary outcomes, and examining risk in subgroups of women. The apparent slight increase in risk occurred predominantly for myocardial infarction, with no material increase in the risk of coronary revascularization, angina, or congestive heart failure.

Although the trend toward a decreasing risk of CHD over time with estrogen plus progestin was statistically significant, these results must be interpreted with caution. Hazard ratios for CHD were above 1.0 through year 5 among women assigned to postmenopausal hormone therapy, with particularly elevated rates in year 1. Results in subsequent years were limited by smaller numbers and lower rates of adherence to study medication and were confined to women who were still at risk for a first coronary event. Thus, results in later years could be artifactually lowered by an acceleration of events in earlier years among susceptible women assigned to postmenopausal hormone therapy. In addition, an increase in the rates of events in the placebo

Table 2. Estrogen plus Progestin and the Risk of CHD, According to Year of Follow-up.*

Year of Follow-up	CHD		Hazard Ratio for CHD (95% CI)
	Estrogen-plus-Progestin Group	Placebo Group	
	<i>no. of cases (annualized percentage)</i>		
1	42 (0.50)	23 (0.29)	1.81 (1.09–3.01)
2	38 (0.45)	28 (0.35)	1.34 (0.82–2.18)
3	19 (0.23)	15 (0.19)	1.27 (0.64–2.50)
4	32 (0.39)	25 (0.32)	1.25 (0.74–2.12)
5	29 (0.41)	19 (0.28)	1.45 (0.81–2.59)
≥ 6	28 (0.37)	37 (0.56)	0.70 (0.42–1.14)

* CHD includes acute myocardial infarction (MI) necessitating hospitalization, silent myocardial infarction as determined by serial electrocardiography, and death due to CHD. There were nine silent myocardial infarctions (four in the estrogen-plus-progestin group and five in the placebo group). Hazard ratios are stratified according to age, presence or absence of a previous coronary event, and randomly assigned diet-modification group and are adjusted for previous coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty. The z score for trend was -2.36 ($P=0.02$); the test for trend was based on Cox proportional-hazards models with time-dependent treatment effects. The 95 percent confidence intervals (CIs) are nominal.

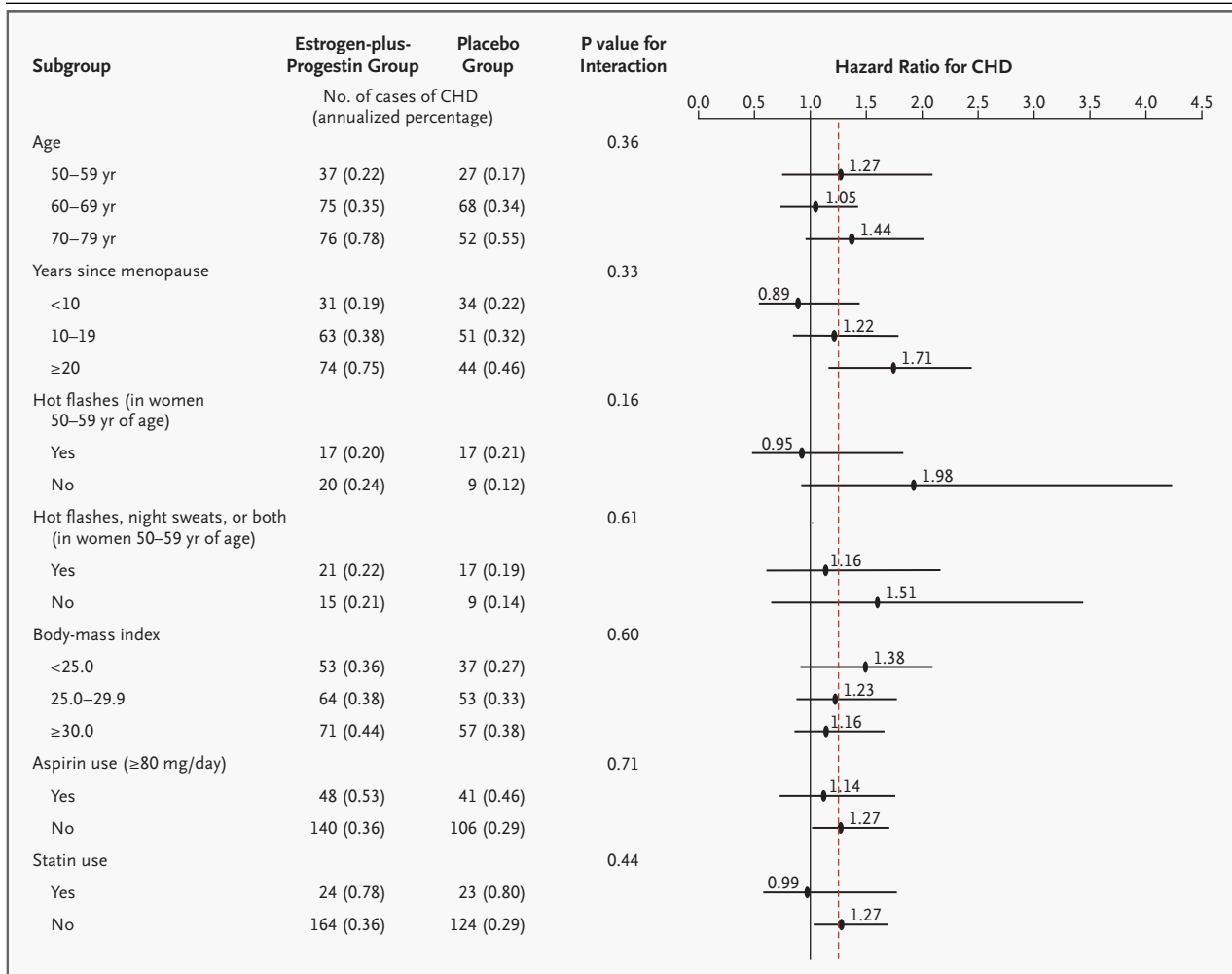


Figure 3. Estrogen plus Progestin and the Risk of CHD in Various Subgroups.

CHD includes nonfatal myocardial infarction and death due to CHD. Hazard ratios are adjusted for age (except for those associated with age and years since menopause) and the presence or absence of CHD at base line. Horizontal bars represent nominal 95 percent confidence intervals. The red dotted vertical line represents the hazard ratio for CHD in the overall cohort. Because of missing data on some variables, the numbers of cases do not always add up to the total number of cases in the treatment group.

group contributed to the apparently lower hazard ratio in year 6 and beyond. Moreover, the increased risk of breast cancer with a longer duration of treatment⁸ and the adverse overall benefit-to-risk profile would outweigh any coronary benefit that might be seen with longer follow-up.

No subgroup of women except those with higher base-line LDL cholesterol levels had evidence of a risk of CHD with estrogen plus progestin that differed significantly from that observed for all women, and the findings related to LDL cholesterol may have been due to chance. Age, time since menopause, body-mass index, presence or absence of

vasomotor symptoms at base line, coronary-risk-factor status, and other variables were not significantly related to the risk of CHD with hormone therapy. Base-line levels of C-reactive protein, fibrinogen, and other biomarkers also did not appear to modulate the risk. None of these variables should be used at this time for risk stratification or for the identification of women who may be more or less vulnerable to an adverse coronary outcome when given hormone therapy.

The absence of the provision of cardiac protection by estrogen plus progestin in our study is consistent with recent findings from randomized tri-

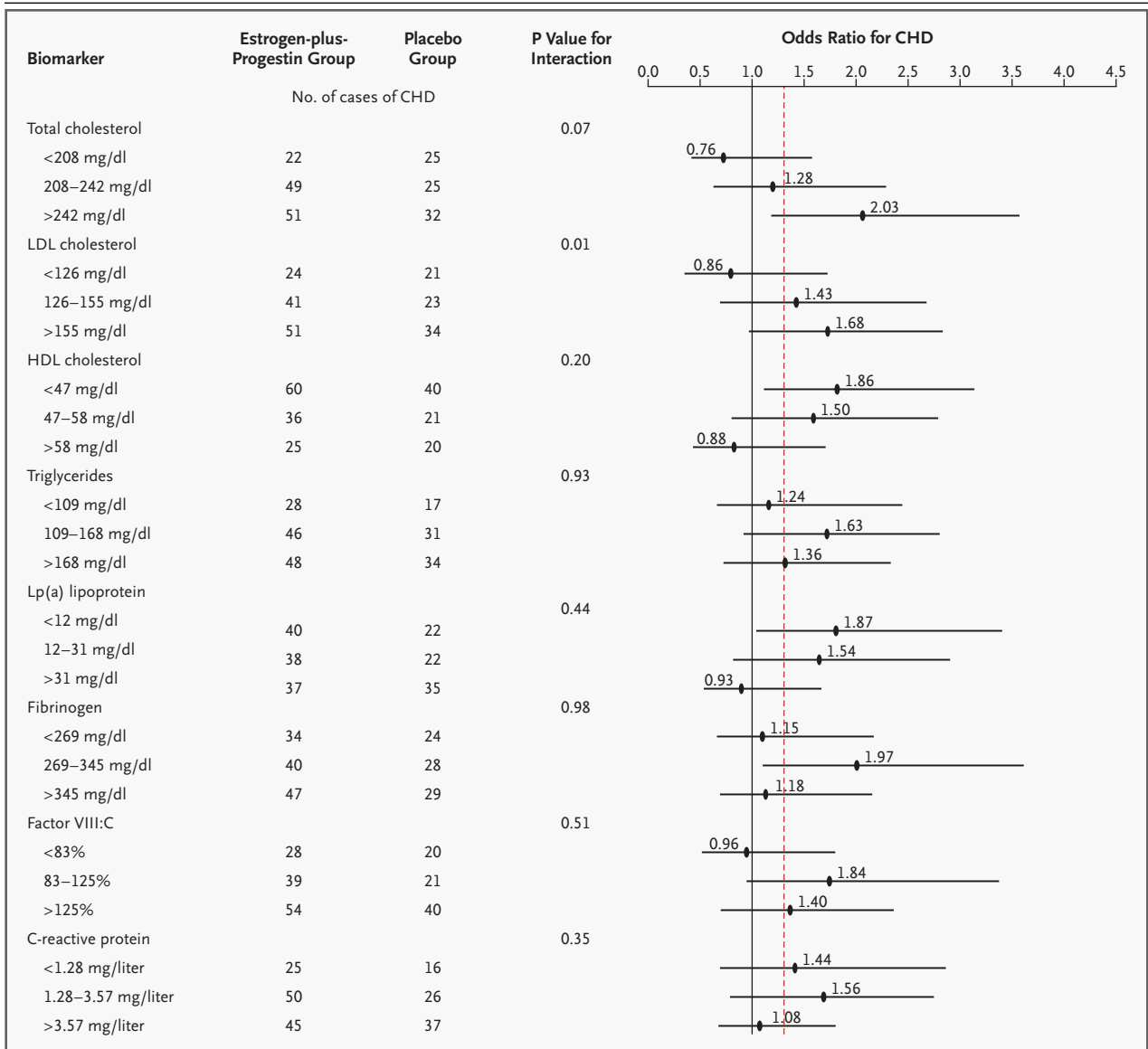


Figure 4. Estrogen plus Progestin and the Risk of CHD According to Levels of Biomarkers at Base Line.

In the nested case-control study, the women were divided into three groups of approximately equal size on the basis of their values for each variable. Log-transformed biomarker values were used, with a likelihood-ratio statistic with two degrees of freedom. Odds ratios (with the placebo group within each subgroup used as the reference group) are adjusted for age, year of randomization, and presence or absence of CHD at base line; in addition, odds ratios associated with lipid variables are adjusted for the use or nonuse of statin therapy. Horizontal lines represent the nominal 95 percent confidence intervals. The red dotted vertical line represents the overall odds ratio for CHD among women in the biomarker substudy. Differences between groups in total cholesterol and lipid subfractions, factor VIII:C, and C-reactive protein were statistically significant predictors ($P < 0.05$) of the risk of CHD in the cohort. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

Table 3. Estrogen plus Progestin and the Risk of CHD in Various Subgroups.*

Variable	CHD		Adjusted Hazard Ratio (95% CI)	P Value for Interaction
	Estrogen-plus-Progestin Group	Placebo Group		
	<i>no. of cases (annualized percentage)</i>			
Race or ethnic group				0.41
Non-Hispanic white	165 (0.41)	124 (0.33)	1.28 (1.02–1.62)	
Non-Hispanic black	13 (0.42)	10 (0.32)	1.22 (0.53–2.81)	
Hispanic	6 (0.24)	4 (0.18)	1.33 (0.37–4.75)	
Level of education				0.86
≤High school or GED	63 (0.51)	50 (0.42)	1.26 (0.87–1.83)	
>High school	124 (0.35)	96 (0.29)	1.22 (0.94–1.60)	
Cigarette smoking				0.64
Never smoked or former smoker	153 (0.36)	116 (0.29)	1.27 (1.00–1.62)	
Current smoker	31 (0.63)	25 (0.53)	1.10 (0.64–1.87)	
Hypertension				0.49
No	81 (0.26)	66 (0.23)	1.14 (0.82–1.58)	
Yes	107 (0.65)	81 (0.50)	1.32 (0.99–1.76)	
Diabetes				0.51
No	155 (0.34)	123 (0.29)	1.20 (0.94–1.52)	
Yes, medication-treated	27 (1.33)	22 (1.15)	1.31 (0.73–2.34)	
Yes (all cases)	32 (1.20)	24 (0.96)	1.45 (0.84–2.51)	
No. of risk factors for CHD				0.96
None	20 (0.15)	17 (0.12)	1.19 (0.62–2.28)	
1–2	62 (0.43)	38 (0.27)	1.59 (1.06–2.37)	
≥3	59 (1.24)	52 (1.12)	1.15 (0.79–1.68)	
Presence of cardiovascular disease at base line				0.64
No	156 (0.34)	118 (0.28)	1.23 (0.97–1.56)	
Yes	29 (1.64)	24 (1.19)	1.45 (0.84–2.49)	
Presence of CHD at base line				0.66
No	163 (0.35)	124 (0.29)	1.23 (0.97–1.55)	
Yes	22 (2.18)	18 (1.65)	1.44 (0.77–2.70)	

* CHD includes nonfatal myocardial infarction and death due to CHD. Hazard ratios (with nominal 95 percent confidence intervals [CIs]) are adjusted for age and the presence of CHD at base line. P values are for the interaction between the subgroup variable and treatment. Hypertension was defined as treated hypertension or a measured blood pressure of 140/90 mm Hg or higher. Risk factors for CHD included current cigarette smoking, hypertension, diabetes, high cholesterol levels, and a parental history of myocardial infarction (at <55 years of age in the father or <65 years of age in the mother). The presence of cardiovascular disease at base line was defined as a history of myocardial infarction, coronary-artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), stroke, or transient cerebral ischemia. The presence of CHD at base line was defined as a history of myocardial infarction, CABG, or PTCA. Because of missing data on some variables, the numbers of cases do not always add up to the total number of cases in the treatment group. GED denotes general equivalency diploma.

als of postmenopausal hormone therapy in women with CHD. In the Heart Estrogen/Progestin Replacement Study (HERS), estrogen plus progestin had no overall effect on the risk of recurrent coronary events after 4.1³ and 6.8²¹ years of follow-up, although the finding of an increased risk after the initiation of treatment was similar to findings in our study. In two angiographic trials,^{4,6} neither estrogen plus progestin nor estrogen alone was associated with inhibition of the progression of coronary atherosclerosis. The Papworth trial,⁵ which tested transdermal 17 β -estradiol with or without norethindrone, and a trial of estradiol valerate (without progestin) in women with a history of myocardial infarction²² also demonstrated no cardioprotection with postmenopausal hormone therapy. Moreover, the Women's Estrogen for Stroke Trial, which tested oral 17 β -estradiol (without progestin), found no overall effect of estrogen on the risk of recurrent stroke and an increase in the risk of fatal stroke.²³ Thus, although most of these trials tested the hormone regimen we studied (oral conjugated equine estrogen and medroxyprogesterone acetate), the trials testing transdermal or oral 17 β -estradiol or estradiol valerate had similar results.

Previous randomized trials have elucidated several favorable and unfavorable effects of exogenous hormone therapy on intermediate biomarkers. Estrogen therapy reduces plasma levels of LDL cholesterol and increases levels of HDL cholesterol, improves endothelial vascular function, and reduces the levels of fibrinogen, Lp(a) lipoprotein, plasminogen-activator inhibitor type 1, and insulin.^{11,12,24,25} However, estrogen also has adverse physiological effects, including increasing the plasma levels of triglycerides; small, dense LDL particles; C-reactive protein; and thrombotic markers such as factor VII, prothrombin fragment 1+2, and fibrinopeptide A.^{11,12,26,27} The addition of a progestin attenuates some of the lipid benefits of estrogen, particularly the increase in HDL cholesterol, but does not seem to counter the prothrombotic effects.^{12,24}

Whether or not certain clinical characteristics of the study population or base-line levels of selected biomarkers predict the coronary effects of postmenopausal hormone therapy is an important area of inquiry. Previous trials have identified few factors that modulate risk. In the HERS trial, despite extensive subgroup analyses, results were found to be generally similar regardless of age and coronary-risk-factor status.^{3,21,28} Hormone therapy appeared to have a less adverse coronary effect on women who

were taking statins than on those who were not, but the differences were not significant.²¹ Although the findings are of interest in view of antiinflammatory and C-reactive-protein-lowering effects of statins,²⁹ the available data do not support the use of such agents to attenuate the risk of CHD associated with postmenopausal hormone therapy unless and until clinical trials demonstrate such a benefit. Finally, the results of HERS suggested a possible reduction in the risk of CHD with hormone therapy among women with elevated base-line Lp(a) lipoprotein levels¹³; we did not observe clear evidence of cardiac protection by postmenopausal hormone therapy in this subgroup.

Some limitations of our trial deserve consideration. The WHI tested only a single regimen of estrogen plus progestin. Thus, our results do not necessarily apply to other formulations, doses, or routes of administration of these hormones, and the trial could not distinguish the effects of estrogen from those of progestin. However, randomized trials of oral or transdermal estrogen alone, to date, have had results similar to those of the WHI with regard to CHD.^{4-6,22} Another limitation is the relatively high rate of discontinuation of hormone therapy in the trial, which tends to decrease the observed treatment effects and may lead to an underestimate of adverse cardiovascular effects. Finally, because of the small size of many of the subgroups examined (which limits the statistical power to detect interactions) and the number of comparisons made (approximately 36 tests for interaction), the findings should be interpreted with caution.

In conclusion, our trial documents that estrogen

plus progestin does not have a beneficial effect on the risk of CHD among healthy postmenopausal women. Overall, the risks of treatment outweighed the benefits during 5.6 years of treatment. In view of the combined excess risk of CHD, stroke, venous thromboembolism, and breast cancer, which was not offset by the reduced risk of hip fracture and colorectal cancer,⁸ this treatment is not a viable intervention for primary prevention. Estrogen-plus-progestin therapy should not be initiated or continued for the prevention of cardiovascular disease. These conclusions are consistent with those of recently published guidelines.³⁰⁻³² The trial did not address the role of estrogen plus progestin for the short-term treatment of menopausal symptoms, which remains the only clear indication for the use of this regimen.^{10,31} Information provided in this report about subgroups of women are exploratory and provide direction for future inquiry. In the interim, women with indications for treatment, such as menopausal symptoms, need to consider with their clinicians the suggestion of a slight overall increase in the risk of CHD and information on the risks of other outcomes in making decisions about the use of estrogen-plus-progestin therapy.

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APPENDIX

The following persons are investigators in the Women's Health Initiative: *Program Office* (National Heart, Lung, and Blood Institute, Bethesda, Md.): B. Alving, J.E. Rossouw, L. Pottern, S. Ludlam, J.A. McGowan. *Clinical Coordinating Center* (Fred Hutchinson Cancer Research Center, Seattle): R. Prentice, G. Anderson, A. LaCroix, R. Patterson, A. McTiernan, B. Cochrane, J. Hunt, L. Tinker, C. Kooperberg, M. McIntosh, C.Y. Wang, C. Chen, D. Bowen, A. Kristal, J. Stanford, N. Urban, N. Weiss, E. White; (Bowman Gray School of Medicine, Winston-Salem, N.C.): S. Shumaker, P. Rautaharju, R. Prineas, M. Naughton; (Medical Research Laboratories, Highland Heights, Ky.): E. Stein, P. Laskarzewski; (University of California at San Francisco, San Francisco): S. Cummings, M. Nevitt, M. Dockrell; (University of Minnesota, Minneapolis): L. Harnack; (McKesson BioServices, Rockville, Md.): F. Cammarata, S. Lindenfelser; (University of Washington, Seattle): B. Psaty, S. Heckbert.

Clinical Centers (Albert Einstein College of Medicine, Bronx, N.Y.): S. Wassertheil-Smoller, W. Frishman, J. Wylie-Rosett, D. Barad, R. Freeman; (Baylor College of Medicine, Houston): J. Hays, R. Young, J. Anderson, S. Lithgow, P. Bray; (Brigham and Women's Hospital, Harvard Medical School, Boston): J. Manson, J. Buring, J.M. Gaziano, K. Rexrode, C. Chae; (Brown University, Providence, R.I.): A.R. Assaf, R. Carleton (deceased), C. Wheeler, C. Eaton, M. Cyr; (Emory University, Atlanta): L. Phillips, M. Pedersen, O. Strickland, M. Huber, V. Porter; (Fred Hutchinson Cancer Research Center, Seattle): S.A.A. Beresford, V.M. Taylor, N.F. Woods, M. Henderson, M. Kestin; (George Washington University, Washington, D.C.): J. Hsia, N. Gaba, J. Ascensao, S. Laowattana; (Harbor-UCLA Research and Education Institute, Torrance, Calif.): R. Chlebowski, R. Detrano, A. Nelson, J. Heiner, J. Marshall; (Kaiser Permanente Center for Health Research, Portland, Ore.): C. Ritenbaugh, B. Valanis, P. Elmer, V. Stevens, N. Karanja; (Kaiser Permanente Division of Research, Oakland, Calif.): B. Caan, S. Sidney, G. Bailey, J. Hirata; (Medical College of Wisconsin, Milwaukee): J. Morley Kotchen, V. Barnabei, T.A. Kotchen, M.A.C. Gilligan, J. Neuner; (MedStar Research Institute, Howard University, Washington, D.C.): B.V. Howard, L. Adams-Campbell, M. Passaro, M. Rainford, T. Agurs-Collins; (Northwestern University, Chicago and Evanston, Ill.): L. Van Horn, P. Greenland, J. Khandekar, K. Liu, C. Rosenberg; (Rush-Presbyterian-St. Luke's Medical Center, Chicago): H. Black, L. Powell, E. Mason; (Stanford Center for Research in Disease Prevention, Stanford University, Stanford, Calif.): M.L. Stefanick, M.A. Hlatky, B. Chen, R.S. Stafford, L.C. Giudice; (State University of New York at Stony Brook, Stony Brook): D. Lane, I. Granek, W. Lawson, G. San Roman, C. Messina; (Ohio State University, Columbus): R. Jackson, R. Harris, D. Frid, W.J. Mysiw, M. Blumenfeld; (University of Alabama at Birmingham, Birmingham): C.E. Lewis, A. Oberman, M.N. Fouad, J.M. Shikany, D. Smith West;

(University of Arizona, Tucson and Phoenix): T. Bassford, J. Mattox, M. Ko, T. Lohman; (University at Buffalo, Buffalo, N.Y.): M. Trevisan, J. Wactawski-Wende, S. Graham, J. Chang, E. Smit; (University of California at Davis, Sacramento): J. Robbins, S. Yasmeen, K. Lindfors, J. Stern; (University of California at Irvine, Orange): A. Hubbell, G. Frank, N. Wong, N. Greep, B. Monk; (University of California at Los Angeles, Los Angeles): H. Judd, D. Heber, R. Elashoff; (University of California at San Diego, La Jolla and Chula Vista): R.D. Langer, M.H. Criqui, G.T. Talavera, C.F. Garland, R.E. Hanson; (University of Cincinnati, Cincinnati): M. Gass, S. Wernke, N. Watts; (University of Florida, Gainesville and Jacksonville): M. Limacher, M. Perri, A. Kaunitz, R.S. Williams, Y. Brinson; (University of Hawaii, Honolulu): D. Curb, H. Petrovitch, B. Rodriguez, K. Masaki, S. Sharma; (University of Iowa, Iowa City and Davenport): R. Wallace, J. Torner, S. Johnson, L. Snetselaar, B. VanVoorhis; (University of Massachusetts, Fallon Clinic, Worcester): J. Ockene, M. Rosal, I. Ockene, R. Yood, P. Aronson; (University of Medicine and Dentistry of New Jersey, Newark): N. Lasser, N. Hymowitz, V. Lasser, M. Safford, J. Kostis; (University of Miami, Miami): M.J. O'Sullivan, L. Parker, R. Estape, D. Fernandez; (University of Minnesota, Minneapolis): K.L. Margolis, R.H. Grimm, D.B. Hunninghake, J. LaValleur, K.M. Hall; (University of Nevada, Reno): R. Brunner, S. St. Jeor, W. Graettinger, V. Oujevolk; (University of North Carolina, Chapel Hill): G. Heiss, P. Haines, D. Ontjes, C. Sueta, E. Wells; (University of Pittsburgh, Pittsburgh): L. Kuller, A. Caggiula, J. Cauley, S. Berga, N.C. Milas; (University of Tennessee, Memphis): K.C. Johnson, S. Satterfield, R.W. Ke, J. Vile, F. Tykavsky; (University of Texas Health Science Center, San Antonio): R. Brzyski, R. Schenken, J. Trabal, M. Rodriguez-Sifuentes, C. Mouton; (University of Wisconsin, Madison): C. Allen, D. Laube, P. McBride, J. Mares-Perlman, B. Loevinger; (Wake Forest University School of Medicine, Winston-Salem, N.C.): G. Burke, R. Crouse, L. Parsons, M. Vitolins; (Wayne State University School of Medicine, Hutzel Hospital, Detroit): S. Hendrix, M. Simon, G. McNeeley, P. Gordon, P. Makela.

REFERENCES

- Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiovasc Dis* 1995;38:199-210.
- Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016-37.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women: Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-13.
- Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9.
- Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofield PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *BJOG* 2002;109:1056-62.
- Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-40.
- Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
- Risks of postmenopausal hormone replacement. *JAMA* 2002;288:2819-25.
- Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003;348:645-50.
- Manson JE, Martin KA. Postmenopausal hormone-replacement therapy. *N Engl J Med* 2001;345:34-40.
- Chae CU, Manson JE. Postmenopausal hormone replacement therapy. In: Hennekens CH, ed. *Clinical trials in cardiovascular disease: a companion to Braunwald's Heart Disease*. Philadelphia: W.B. Saunders, 1999: 399-414.
- Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. *JAMA* 2000; 283:1845-52.
- Psaty BM, Smith NL, Lemaitre RN, et al. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001;285:906-13.
- Design of the Women's Health Initiative clinical trial and observational study: the Women's Health Initiative Study Group. *Control Clin Trials* 1998;19:61-109.
- Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The Novacode criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol* 1998;31(3): 157-87.
- Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol* 1995;5:278-85.
- Wassertheil-Smoller S, Hendrix S, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative. *JAMA* 2003;289: 2673-84.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Pilon D, Castilloux AM, Leloirier J. Estrogen replacement therapy: determinants of persistence with treatment. *Obstet Gynecol* 2001;97:97-100.
- Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57. [Erratum, *JAMA* 2002;288:1064.]
- Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002; 360:2001-8.
- Viscoli CM, Brass LM, Kernan WN, Sarrrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9.
- Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199-208. [Erratum, *JAMA* 1995;274:1676.]
- Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340:1801-11.
- Cushman M, Meilahn EN, Psaty BM, Kuller LH, Dobs AS, Tracy RP. Hormone replacement therapy, inflammation, and hemostasis in elderly women. *Arterioscler Thromb Vasc Biol* 1999;19:893-9.
- Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999; 100:717-22.
- Furberg CD, Vittinghoff E, Davidson M, et al. Subgroup interactions in the Heart and Estrogen/Progestin Replacement Study: lessons learned. *Circulation* 2002;105:917-22.
- Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; 286:64-70.
- Mosca L, Collins P, Herrington DM, et al. Hormone replacement therapy and cardiovascular disease: a statement for health-care professionals from the American Heart Association. *Circulation* 2001;104: 499-503.
- The North American Menopause Society (NAMS). Report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy. Cleveland: North American Menopause Society, October 3, 2002.
- U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. *Ann Intern Med* 2002;137:834-9.

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