

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

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Context.—Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective.—To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.

Design.—Randomized, blinded, placebo-controlled secondary prevention trial.

Setting.—Outpatient and community settings at 20 US clinical centers.

Participants.—A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention.—Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily ($n = 1380$) or a placebo of identical appearance ($n = 1383$). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.

Main Outcome Measures.—The primary outcome was the occurrence of non-fatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results.—Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P < .001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38).

Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

MANY OBSERVATIONAL studies have found lower rates of coronary heart disease (CHD) in women who take postmenopausal estrogen than in women not receiving this therapy.¹⁻⁵ This association has been reported to be especially strong for secondary prevention in women with CHD, with hormone users having 35% to 80% fewer recurrent events than nonusers.⁶⁻¹² If this association is causal, estrogen therapy could be an

For editorial comment see p 650.

important method for preventing CHD in postmenopausal women. However, the observed association between estrogen therapy and reduced CHD risk might be attributable to selection bias if women who choose to take hormones are healthier and have a more favorable CHD profile than those who do not.¹³⁻¹⁵ Observational studies cannot resolve this uncertainty.

Only a randomized trial can establish the efficacy and safety of postmenopausal hormone therapy for preventing CHD.

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A complete list of the HERS Research Group participants appears at the end of this article.

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The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, double-blind, placebo-controlled trial of daily use of conjugated equine estrogens plus medroxyprogesterone acetate (progestin) on the combined rate of nonfatal myocardial infarction (MI) and CHD death among postmenopausal women with coronary disease. We enrolled women with established coronary disease because their high risk for CHD events and the strong reported association between hormone use and risk of these events make this an important and efficient study population in which to evaluate the effect of hormone therapy.

METHODS

Study Participants

The design, methods, and baseline findings of the study have been published.¹⁶ Briefly, participants were postmenopausal women younger than 80 years with established coronary disease who had not had a hysterectomy. Postmenopausal was defined as age at least 55 years and no natural menses for at least 5 years, or no natural menses for at least 1 year and serum follicle-stimulating hormone (FSH) level more than 40 IU/L, or documented bilateral oophorectomy, or reported bilateral oophorectomy with FSH level more than 40 IU/L and estradiol level less than 92 pmol/L (25 pg/mL). Established coronary disease was defined as evidence of 1 or more of the following: MI, coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of 1 or more major coronary arteries.

Women were excluded for the following reasons: CHD event within 6 months of randomization; serum triglyceride level higher than 3.39 mmol/L (300 mg/dL); use of oral, parenteral, vaginal, or transdermal sex hormones within 3 months of the screening visit; history of deep vein thrombosis or pulmonary embolism; history of breast cancer or breast examination or mammogram suggestive of breast cancer; history of endometrial cancer; abnormal uterine bleeding, endometrial hyperplasia, or endometrium thickness greater than 5 mm on baseline evaluation; abnormal or unobtainable Papanicolaou test result; serum aspartate aminotransferase level more than 1.2 times normal; unlikely to remain geographically accessible for study visits for at least 4 years; disease (other than CHD) judged likely to be fatal within 4 years; New York Heart Association class IV or severe class III congestive heart failure; alcoholism or other drug abuse; uncontrolled hypertension (diastolic blood pressure ≥ 105 mm Hg or systolic blood pressure ≥ 200 mm Hg);

uncontrolled diabetes (fasting blood glucose level ≥ 16.7 mmol/L [300 mg/dL]); participation in another investigational drug or device study; less than 80% compliance with a placebo run-in prior to randomization; or history of intolerance to hormone therapy.

Baseline Measurements

At 2 baseline clinic visits we collected data on demographic characteristics, reproductive and health history, risk factors for CHD, quality of life, and medication use. Participants had a clinical examination, including breast examination and pelvic examination with Papanicolaou test and endometrial evaluation (endometrial aspiration biopsy if possible or otherwise transvaginal ultrasound measurement of endometrial thickness), and a screening mammogram. Standardized 12-lead electrocardiograms (ECGs) were obtained using the Mac PC (Marquette Electronics, Milwaukee, Wis) and transmitted electronically to EPICARE (Wake Forest University School of Medicine, Winston-Salem, NC) where they were analyzed using computer protocols.¹⁷ Fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined by the Lipoprotein Analytical Laboratory at Johns Hopkins Hospital.¹⁸

Randomization and Blinding

The randomization code was prepared using computer-generated random numbers. Eligible participants were assigned with equal probability to the 2 treatment groups using tamper-proof blocked randomization stratified by clinical center. At each center, women who met the entry criteria were logged and assigned the next available sequential randomized treatment assignment.

Study medication consisted of 1 tablet daily containing both conjugated equine estrogens, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (estrogen plus progestin [Prempro]), or 1 placebo tablet of identical appearance. Chemical analysis of tablets confirmed the composition of the tablets and the accuracy of the blinded medication assignment.

With the exception of 3 persons at the Coordinating Center at the University of California, San Francisco, who prepared analyses for the Data and Safety Monitoring Board and for the final report, investigators and staff at the clinical centers, Wyeth-Ayerst Research, the Coordinating Center, and the independent Morbidity and Mortality Subcommittee were blinded to individual participant assignment throughout the study. To prevent unblinding of clinical center staff, breast discomfort

and vaginal bleeding were reported directly to gynecology staff who were located separate from the clinical center, did not communicate with clinical center personnel about gynecologic symptoms, and did not participate in ascertainment of cardiovascular outcomes. Sealed treatment allocation envelopes were available to the study center gynecologist. To determine if endometrial biopsy was necessary, the gynecologists could open a treatment assignment envelope in limited, defined situations with prior approval of a Coordinating Center physician. Unblinding in this fashion, generally to assist in the management of persistent vaginal bleeding, occurred in 34 women (30 in the hormone group, among whom 1 primary CHD event occurred).

Follow-up

Follow-up visits to the clinical center occurred every 4 months to assess and enhance compliance, provide study medication refills, and obtain outcome and adverse event data. Annual evaluations at the clinical center included general and cardiac examinations, an ECG, and venipuncture at the first, third, and final annual visits. Separate annual follow-up visits to the study gynecologist included repeat breast examination, pelvic examination with Papanicolaou test, screening mammogram, and a repeat endometrial evaluation at the second and final annual visits.

We used extensive quality assurance procedures for clinical management and data collection. All procedures were defined by the Coordinating Center in the HERS procedure manual, with formalized updates and clarifications. The Coordinating Center monitored the degree to which procedures at the clinics conformed with those described in the procedure manual during annual site visits. All data were entered twice and checked by computer algorithms.

Study treatment was discontinued (but follow-up continued) for women who developed any of the following conditions: simple endometrial hyperplasia without atypia that did not respond to treatment with progestin; endometrial hyperplasia with atypia; endometrial, cervical, breast, or ovarian cancer; deep vein thrombosis; pulmonary embolism; prolonged immobilization; or active gallbladder disease.

Outcome Ascertainment

The CHD events (nonfatal MI or CHD death) that occurred between the date of randomization and the closeout date were the primary outcome of the trial; nonfatal MI could be either symptomatic or silent, and CHD death could be a fatal documented MI, sudden death within 1 hour of onset of symptoms, un-

observed death that occurred out of the hospital in the absence of other known cause, or death due to coronary revascularization procedure or congestive heart failure. The diagnosis of nonfatal MI was based on an algorithm¹⁶ that took into account 3 categories of clinical information from the acute event: ischemic symptoms, ECG abnormalities, and elevated cardiac enzyme levels. The diagnosis could also be made if there was evidence of fresh MI at autopsy. All ECGs obtained electronically were compared with the ECG obtained at baseline for changes indicating new MI.

Secondary cardiovascular outcomes included coronary artery bypass graft surgery, percutaneous coronary revascularization, hospitalization for unstable angina, resuscitated cardiac arrest, congestive heart failure, stroke or transient ischemic attack, and peripheral arterial disease. Other prespecified secondary outcomes were total mortality; cancer death; non-CHD, noncancer death; breast, endometrial, and other cancer; deep vein thrombosis; pulmonary embolism; hip and other fracture; and gallbladder disease.¹⁶

The primary and secondary outcomes of HERS were addressed at each follow-up contact. Suspected outcome events were reported within 24 hours to the Coordinating Center, which had primary responsibility for the outcome database, and to Wyeth-Ayerst Research as a cross-check. Clinics obtained and sent to the Coordinating Center specified documentation that included (depending on the suspected event) hospital discharge summaries, ECGs, cardiac enzyme levels and other test results, and reports of tissue pathology, procedures, and x-ray examinations. Data from all deaths and suspected primary outcome events were reviewed and classified according to prespecified criteria by an independent Morbidity and Mortality Subcommittee blinded to treatment assignment. Secondary events were classified by Coordinating Center physicians blinded to treatment assignment. Every event (whether primary or secondary) was classified independently by 2 reviewers, and discordant classifications were resolved in discussions between the reviewers. Problematic potential primary events were discussed on conference calls or meetings involving the entire subcommittee.

Vital status is known for all 2763 women, and all deaths are included in this report. We are still in the process of collecting hospital records and adjudicating recent events. Included in this report are 99% of all primary CHD events reported to have occurred by the closeout visit (April-July 1998) and 97% of all secondary events. Adjudication is final

for 96% of included primary events (the remaining classifications are provisional), and it is final for 99% of included secondary events.

Statistical Power and Analyses

We estimated that we needed to enroll 2340 women, assuming a primary CHD event rate in the placebo group of 5% per year, a combined non-CHD death and loss to follow-up rate of 2% per year, crossovers from active to placebo of 5%, 4%, and 3% in the first 3 years and 2% per year thereafter, crossovers from placebo to active of 1% each year, and average follow-up of 4.75 years.¹⁶ We assumed that half the reduction in primary CHD events would operate through nonlipid mechanisms (and therefore be immediate), and half would operate through lipid changes (and therefore begin after a 2-year lag period). These assumptions resulted in 90% power at a 2-tailed α of .05 to detect an intention-to-treat effect size of 24%. In the actual study, the event rate was only 3.3%, compliance was less than expected, and treatment duration averaged 4.1 years. The chief reason for the shorter-than-expected treatment duration, despite ending the study at the planned time, was the fact that most women were enrolled toward the end of the recruitment period. The reduction in power caused by these deviations from prestudy assumptions was partially offset by the fact that we recruited 18% more participants than planned.

The primary analysis compares the rate of CHD events among women assigned to active medication with the rate among women assigned to placebo using an unadjusted Cox proportional hazards model for time to first CHD event; this is equivalent to the log rank test. The analysis was by intention to treat, categorizing participants according to randomized treatment assignment regardless of compliance. Participants who asked to drop out of the study and had not had a nonfatal MI were censored for nonfatal events at their last visit (this occurred for 31 women in the hormone group and 38 women in the placebo group); however, vital status was assessed at the end of the trial for 100% of the cohort, and all deaths are included in this report.

Secondary analyses used multivariate proportional hazards models to investigate study findings. Possible confounding was examined by controlling for important baseline covariates. To identify potential postrandomization confounders, treatment effect estimates were compared in nested models with and without measures of postrandomization lipid-lowering drug use and lipid change. These covariates were also included in an as-treated model, where inclusion in

the risk sets was limited to women in both treatment groups whose average pill-count compliance since randomization was at least 80%; this model included 74% of the primary events. Relative hazards were estimated by year since randomization (censoring women with events in earlier years), and continuous trend in the log relative hazard was examined in a companion model. Time-dependent indicators were used to assess risk by treatment assignment among women who had recently stopped taking study medication.

Data and Safety Monitoring Board

Interim monitoring of study events every 3 to 6 months was performed by an independent HERS Data and Safety Monitoring Board. Early in the trial the board noted adverse trends in primary CHD events, which conflicted with existing evidence and did not cross the stopping boundaries.¹⁹ In the middle years of the trial, an increased risk of venous thromboembolic events in the hormone-treated group consistent with existing evidence did cross the stopping boundaries. As a consequence, the board advised HERS investigators to report the findings regarding increased risk of venous thrombosis and to institute additional measures to reduce risk in HERS participants.²⁰ Near the end of the trial, the board noted a trend toward lower rates of nonfatal MI in the hormone group. At its final meeting in December 1997, the board recommended against continuing the study beyond the scheduled closeout date, because at that time conditional power estimates for primary CHD events were low and because of uncertainty about whether a sufficient proportion of women would consent to continue blinded treatment. The board recommended closeout at the originally planned time (April-July 1998), continuation of disease event surveillance, and rapid publication of the findings to allow HERS participants to make timely informed decisions concerning their use of this specific hormone therapy.

RESULTS

Between January 1993 and September 1994, the 20 HERS clinical centers enrolled 2763 women; 1380 were assigned to the hormone group and 1383 to the placebo group (Figure 1). Participants ranged in age from 44 to 79 years, with a mean of 66.7 years (SD, 6.7 years) at baseline. Most participants were white (89%) and had completed high school (80%). Examination of the distribution of these and other variables revealed no significant differences between the treatment groups at baseline (Table 1).

Table 1.—Baseline Characteristics of HERS Participants (n=2763) by Treatment Group*

Characteristic	Treatment Group		P Value
	Estrogen-Progestin (n=1380)	Placebo (n=1383)	
Demographics			
Age, mean±SD, y	67±7	67±7	.32
White, %	88	90	.14
Education, mean±SD, y	13±3	13±3	.84
CHD risk factors			
Current smoker, %	13	13	.84
Diabetes on oral medication or insulin, %	19	18	.44
Systolic blood pressure, mean±SD, mm Hg	135±19	135±19	.88
Diastolic blood pressure, mean±SD, mm Hg	73±10	73±10	.89
LDL cholesterol, mean±SD, mmol/L (mg/dL)	3.75±0.96 (145±37)	3.75±0.98 (145±38)	.83
HDL cholesterol, mean±SD, mmol/L (mg/dL)	1.29±0.34 (50±13)	1.29±0.34 (50±13)	.41
Triglyceride, mean±SD, mmol/L (mg/dL)	1.90±0.72 (168±64)	1.86±0.72 (165±64)	.25
Time since last menstrual period, mean ± SD, y	18±8	18±8	.31
Body mass index >27 kg/m ² , %	57	55	.44
Exercise >3 times weekly, %	39	38	.72
No. of drinks per week, mean±SD	1.4±4	1.3±4	.83
General health poor or fair, %	24	24	.94
Postmenopausal estrogen use, %†	24	23	.43
CHD manifestations			
Signs of congestive heart failure, %‡	10	9	.38
Q-wave myocardial infarction, %	17	17	.94
Percutaneous coronary revascularization, %	45	45	.96
Coronary artery bypass graft surgery, %	42	41	.64
Medication use			
Aspirin, %	78	78	.73
β-Blockers, %	33	32	.72
Lipid-lowering medications, %	45	47	.26
Calcium channel blockers, %	55	55	.83
Angiotensin-converting enzyme inhibitors, %	17	18	.57
Diuretics, %	28	28	.79
Multivitamins, %	29	30	.45

*HERS indicates Heart and Estrogen/progestin Replacement Study; CHD, coronary heart disease; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. P values are for difference between treatment groups by t test or χ^2 .

†Estrogen use refers to use after menopause but not within 3 months of HERS screening.

‡Presence of jugular venous distention more than 8 cm H₂O, S₃ heart sound, rales, or pitting peripheral edema.

At the end of the first year, the proportion who reported taking study medication was 82% in the hormone group and 91% in the placebo group; by the end of the third year, these proportions had declined to 75% and 81%. Pill counts revealed 79% of the women in the hormone group to be taking at least 80% of their study medication at the end of year 1 and 70% to be doing so at the end of year 3 (Figure 2). Among women who stopped taking HERS medications, 110 (8%) of those assigned to the placebo group and 36 (3%) of those assigned to the hormone group reported taking open-label oral or transdermal estrogen.

During the closeout period (April-July 1998), vital status was ascertained for all 2763 randomized women. Follow-up percentages were nearly the same in the 2 randomized groups (Figure 1).

Primary CHD Outcome

Primary CHD events occurred in 172 women in the hormone group (33.1/1000 women per year) and in 176 women in the placebo group (33.6/1000 women per

year) (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22) (Table 2). These primary events were composed of CHD deaths (RH, 1.24; 95% CI, 0.87-1.75) and nonfatal MIs (RH, 0.91; 95% CI, 0.71-1.17). None of these differences was statistically significant. The 71 CHD deaths in the hormone group and the 58 CHD deaths in the placebo group were distributed, respectively, as follows: sudden death within 1 hour of onset of symptoms, 19 and 20; myocardial infarction, 19 and 16; congestive heart failure, 9 and 6; coronary artery bypass graft surgery, 5 and 2; and other CHD death, 19 and 14.

Survival curves for the primary CHD outcome and its components (Figure 3) correspond with the findings in Table 2. The curves for CHD death diverged during the second year of observation. The curves for nonfatal MI diverged during the first year, then converged and crossed during the third year. This possible change in the RH with time since randomization is further examined in Table 3. The point estimates for the primary outcome

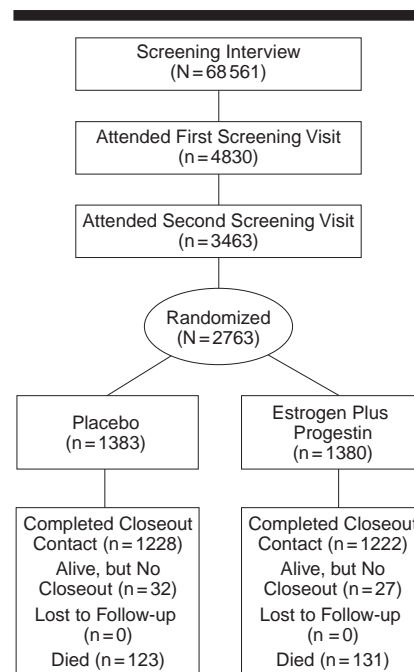


Figure 1.—The Heart and Estrogen/progestin Replacement Study trial profile, showing numbers of participants from screening to closeout.

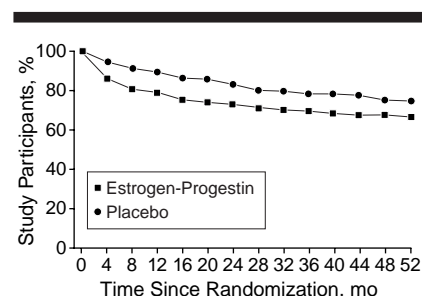


Figure 2.—Participants taking protocol medications and with pill count of 80% or more, as a percentage of all women at risk for a primary coronary heart disease event.

in the hormone group compared with the placebo group are 1.52 in year 1, 1.00 in year 2, 0.87 in year 3, and 0.67 in years 4 and 5 ($P = .009$ for trend in log RH); within the first year, the RH was 2.30 for the first 4 months, 1.46 for the second 4 months, and 1.18 for the third 4 months ($P = .33$ for trend). The difference over time was most pronounced for the nonfatal MI component of the primary CHD outcome (Table 3 and Figure 3).

In an as-treated analysis limited to women who had been at least 80% compliant with study medication by pill count, the RH comparing the primary CHD outcome in the hormone and placebo groups was 0.87 (95% CI, 0.67-1.11), lower than the intention-to-treat analysis but not statistically significant. For women who stopped taking HERS medication, risk of primary CHD events was elevated in the

first month after stopping use of the medication. However, there was no difference by group (RH in hormone group, 7.28; 95% CI, 4.45-11.93; RH in placebo group, 7.40; 95% CI, 4.23-12.95), suggesting that illness caused both the discontinuation of medication and the CHD event.

The RH comparing risk of the primary CHD outcome in the hormone and placebo groups was similar after adjusting for the small and nonsignificant differences between the groups in age and other baseline CHD risk factors (RH, 0.95; 95% CI, 0.76-1.17). We sought to identify differential effects of estrogen plus progestin therapy in women classified by baseline variables such as older age, ill health, history of MI, and so forth. There was no clear evidence of differential effects in 86 subgroups categorized by all the variables presented in Table 1 and others.

Other Cardiovascular Outcomes

There were no statistically significant differences between the randomized

groups in any of the other cardiovascular outcomes that we evaluated (Table 2). The survival curve for time to first occurrence of any coronary revascularization procedure or hospitalization for definite unstable angina (Figure 4) appeared to diverge, with lower rates in the hormone-treated group, although this difference did not achieve statistical significance (RH, 0.89; $P = .15$).

Plasma Lipids

By the end of the first year of treatment, mean LDL cholesterol levels had decreased by 14% from baseline to a level of 3.23 mmol/L (125 mg/dL) in the hormone group and by 3% to 3.62 mmol/L (140 mg/dL) in the placebo group ($P < .001$ for difference between groups) (Figure 5). During the same period, mean HDL cholesterol levels had increased by 8% to 1.40 mmol/L (54 mg/dL) in the hormone group and decreased by 2% to 1.27 mmol/L (49 mg/dL) in the placebo group ($p < .001$). Mean triglyceride

levels had increased by 10% to 2.04 mmol/L (181 mg/dL) in the hormone group and by 2% to 1.93 (170 mg/dL) in the placebo group ($P < .001$).

In proportional hazards analysis, high LDL cholesterol and low HDL cholesterol levels at baseline predicted subsequent primary CHD events in both univariate and multivariate (controlling for other baseline risk factors) models, but high triglyceride levels predicted primary CHD events only in univariate analyses. Changes in LDL cholesterol, HDL cholesterol, and triglyceride levels over the first year of the study were not significantly associated with subsequent primary CHD events, but the point estimates were in the expected direction and there was limited power to examine this effect.

More women in the placebo group than in the hormone group began treatment with lipid-lowering drugs, primarily statins, during the trial (22% vs 18%; $P = .004$), probably because the higher LDL cholesterol levels in placebo-treated women compared with hormone-treated women were noted by the women's personal physicians. Adjustment for this difference using regression analysis did not substantially change the overall estimate of the between-group difference in risk of primary CHD events (RH, 0.94; 95% CI, 0.76-1.17).

Other Secondary Outcomes

Cancer deaths and other deaths were nearly identical in the 2 study groups. Total mortality in the hormone group was not significantly different from that in the placebo group (131 vs 123 women; RH, 1.08; 95% CI, 0.84-1.38) (Table 4; Figure 6).

Confirmed venous thromboembolic events occurred in 34 women in the hormone group (6.3/1000 woman-years) and

Table 2.—Cardiovascular Outcomes by Treatment Group*

Outcomes	Treatment Group		RH (95% CI)	P Value
	Estrogen-Progestin (n=1380)	Placebo (n=1383)		
Primary CHD events†	172	176	0.99 (0.80-1.22)	.91
CHD death	71	58	1.24 (0.87-1.75)	.23
Nonfatal MI	116	129	0.91 (0.71-1.17)	.46
Other cardiovascular outcomes				
Coronary artery bypass graft surgery	88	101	0.87 (0.66-1.16)	.36
Percutaneous coronary revascularization	164	175	0.95 (0.77-1.17)	.62
Hospitalization for unstable angina	103	117	0.89 (0.68-1.16)	.38
Hospitalization for congestive heart failure	128	112	1.07 (0.84-1.38)	.58
Resuscitated cardiac arrest	19	13	1.48 (0.73-3.00)	.28
Other CHD event	3	1	3.03 (0.32-29.1)	.34
Peripheral arterial disease	94	108	0.87 (0.66-1.15)	.34
Stroke/transient ischemic attack	108	96	1.13 (0.85-1.48)	.40

*RH indicates relative hazard; CI, confidence interval; CHD, coronary heart disease; and MI, myocardial infarction. Each row represents the number of women with the designated event; women with more than 1 type of event may appear in more than 1 row.

†Primary CHD events include coronary death and nonfatal MI. Among the 245 nonfatal MIs, there were 7 silent MIs, found on annual electrocardiogram. There were 26 women with nonfatal MI who subsequently suffered CHD death.

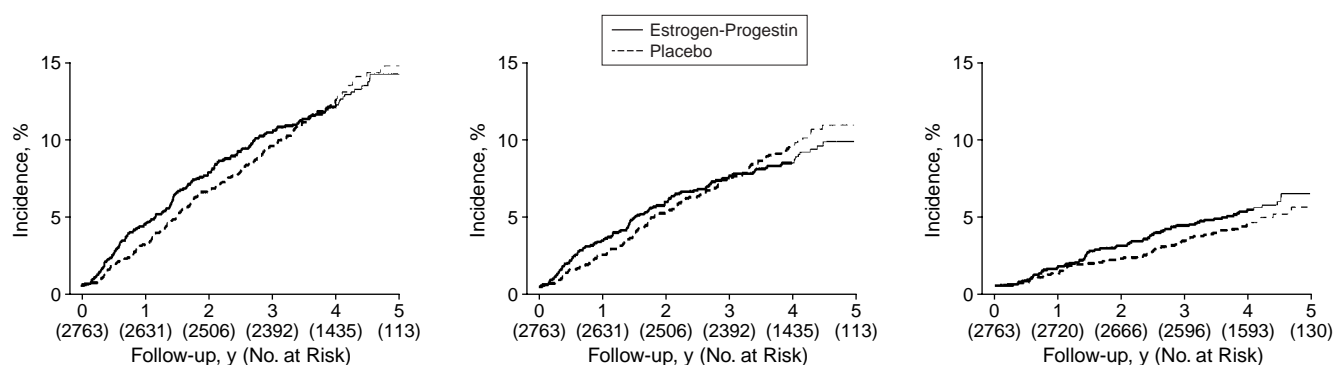


Figure 3.—Kaplan-Meier estimates of the cumulative incidence of primary coronary heart disease (CHD) events (left) and to its constituents: nonfatal myocardial infarction (MI) (center) and CHD death (right). The number of women observed at each year of follow-up and still free of an event are provided in parentheses, and the curves become fainter when this number drops below half of the cohort. Log rank P values are .91 for primary CHD events, .46 for nonfatal MI, and .23 for CHD death.

Table 3.—Outcomes by Treatment Group and Year Since Randomization*

Outcome and Period	Estrogen-Progestin		Placebo		RH (95% CI)	P Value‡
	No.	Rate†	No.	Rate†		
Primary CHD event§						
Year 1	57	42.5	38	28.0	1.52 (1.01-2.29)	.009
Year 2	47	37.0	48	37.1	1.00 (0.67-1.49)	
Year 3	35	28.8	41	33.1	0.87 (0.55-1.37)	
Years 4 and 5	33	23.0	49	34.4	0.67 (0.43-1.04)	
Nonfatal myocardial infarction						
Year 1	42	31.3	29	21.4	1.47 (0.91-2.36)	.01
Year 2	34	26.8	37	28.6	0.94 (0.59-1.49)	
Year 3	20	16.5	29	23.4	0.70 (0.40-1.24)	
Years 4 and 5	20	13.9	34	23.9	0.58 (0.34-1.02)	
CHD death						
Year 1	17	12.5	11	8.0	1.56 (0.73-3.32)	.34
Year 2	19	14.4	13	9.7	1.48 (0.73-2.99)	
Year 3	18	14.0	16	12.3	1.14 (0.58-2.24)	
Years 4 and 5	17	11.0	18	11.6	0.95 (0.49-1.84)	
Unstable angina or coronary revascularization¶						
Year 1	101	77.1	94	71.1	1.08 (0.82-1.44)	.42
Year 2	52	43.3	85	70.6	0.61 (0.43-0.87)	
Year 3	69	61.9	56	50.5	1.22 (0.86-1.74)	
Years 4 and 5	47	36.6	67	54.2	0.67 (0.46-0.98)	
Venous thromboembolic event						
Year 1	13	9.6	4	2.9	3.29 (1.07-10.08)	.28
Year 2	8	6.1	2	1.5	4.09 (0.87-19.27)	
Year 3	7	5.5	3	2.3	2.40 (0.62-9.28)	
Years 4 and 5	6	4.0	3	2.0	2.05 (0.15-8.18)	

*RH indicates relative hazard; CI, confidence interval; and CHD, coronary heart disease.

†Event rates per 1000 women-years in the estrogen plus progestin or placebo group.

‡P values for tests of continuous trend in log-relative hazard.

§Primary CHD events include nonfatal myocardial infarction and CHD death.

¶Coronary revascularization includes coronary artery bypass graft surgery and percutaneous coronary revascularization.

in 12 women in the placebo group (2.2/1000 woman-years) (RH, 2.89; 95% CI, 1.50-5.58; $P = .002$) (Table 4). More women in the hormone group experienced deep vein thromboses (25 vs 8; $P = .004$) and pulmonary emboli (11 vs 4; $P = .08$); 2 of the pulmonary emboli, both in the hormone group, were fatal. The RH in the hormone group relative to the placebo group remained elevated over the 4 years of observation but declined somewhat during the study (Table 3).

Gallbladder disease occurred in 84 women in the hormone group and in 62 women in the placebo group (RH, 1.38; 95% CI, 1.00-1.92). Gallbladder surgery accounted for 89% of these events, and the rest were symptomatic cholelithiasis. None of the gallbladder events was fatal.

There were no significant differences between the treatment groups in the rates of breast cancer, endometrial cancer, other cancers, or fracture (Table 4).

COMMENT

In this clinical trial, postmenopausal women younger than 80 years with established coronary disease who received estrogen plus progestin did not experience a reduction in overall risk of nonfatal MI and CHD death or of other car-

diovascular outcomes. How can this finding be reconciled with the large body of evidence from observational and pathophysiologic studies suggesting that estrogen therapy reduces risk for CHD?

Contrast With Findings of Observational Studies

Observational studies may be misleading because women who take postmenopausal hormones tend to have a better CHD risk profile^{13,21,22} and to obtain more preventive care¹⁴ than nonusers. The consistency of the apparent benefit in the observational studies could simply be attributable to the consistency of this selection bias. The lower rate of CHD in hormone users compared with nonusers persists after statistical adjustment for differences in CHD risk factors,²² but differences in unmeasured factors remain a possible explanation.

The discrepancy between the findings of HERS and the observational studies may also reflect important differences between the study populations and treatments. Most of the observational studies of postmenopausal hormone therapy enrolled postmenopausal women who were relatively young and healthy and who took unopposed estrogen.^{1-3,23} In contrast, participants in

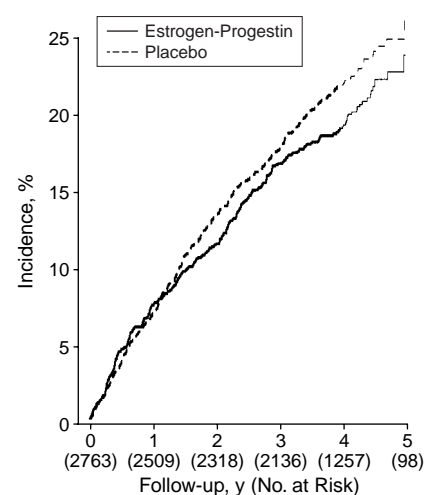


Figure 4.—Kaplan-Meier estimate of the cumulative incidence of definite unstable angina or coronary artery bypass graft or percutaneous coronary revascularization. The number of women observed at each year of follow-up and still free of an event are provided in parentheses, and the curves become fainter when this number drops below half the cohort. Log rank P value is .15.

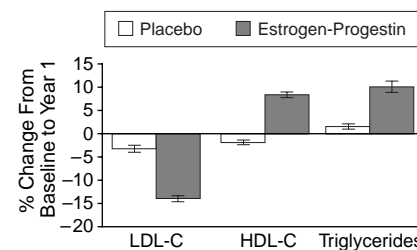


Figure 5.—Mean change in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels during the first year of the study, expressed as percent change \pm SEM.

HERS were older, had coronary disease at the outset, and were treated with estrogen plus progestin. However, some observational studies did examine women with prior CHD, and all of these reported a beneficial association with postmenopausal hormone therapy.⁶⁻¹² Similarly, some observational studies did examine the effect of postmenopausal estrogen plus progestin therapy on CHD risk in women, and these generally report a lower rate of CHD events in hormone users that is similar to that reported for estrogen alone^{4,5,22,24-27}; however, details in these studies about the specific progestin formulations and dosing regimens used are limited.

Possible Adverse Effects of Medroxyprogesterone Acetate

Several potential mechanisms whereby estrogen therapy might reduce risk for CHD have been proposed, including fa-

Table 4.—Death and Secondary Noncardiovascular Outcomes by Treatment Group*

Outcomes	Treatment Group		RH (95% CI)	P Value
	Estrogen-Progestin (n=1380)	Placebo (n=1383)		
Death				
CHD death	71	58	1.24 (0.87-1.75)	.23
Cancer death	19	24	0.80 (0.44-1.46)	.47
Non-CHD, noncancer death	37	36	1.04 (0.66-1.64)	.87
Unadjudicated death	4	5
Total deaths	131	123	1.08 (0.84-1.38)	.56
Venous thromboembolic event				
Deep vein thrombosis	25	8	3.18 (1.43-7.04)	.004
Pulmonary embolism	11	4	2.79 (0.89-8.75)	.08
Any thromboembolic event	34	12	2.89 (1.50-5.58)	.002
Cancer				
Breast	32	25	1.30 (0.77-2.19)	.33
Endometrial	2	4	0.49 (0.09-2.68)	.41
Other	63	58	1.10 (0.77-1.57)	.60
Any cancer	96	87	1.12 (0.84-1.50)	.44
Fracture				
Hip	12	11	1.10 (0.49-2.50)	.82
Other	119	129	0.93 (0.73-1.20)	.59
Any fracture	130	138	0.95 (0.75-1.21)	.70
Gallbladder disease	84	62	1.38 (1.00-1.92)	.05

*RH indicates relative hazard; CI, confidence interval; and CHD, coronary heart disease. Each row represents the number of women with the designated event; women with more than 1 type of event may appear in more than 1 row.

avorable effects on lipoproteins, coronary atherosclerosis, endothelial function, and arterial thrombosis.^{28,29} Progestins down-regulate estrogen receptors and may also have direct, progestin receptor-mediated effects that oppose these actions of estrogen³⁰; medroxyprogesterone acetate may do this to a greater extent than other progestins. In the Postmenopausal Estrogen-Progestin Interventions Trial, medroxyprogesterone acetate blunted the estrogen-associated increase in HDL cholesterol substantially more than did micronized progesterone.³¹ Oral medroxyprogesterone acetate appears to significantly attenuate the beneficial effects of estrogen on coronary atherosclerosis in nonhuman primates,³² while subcutaneous progesterone does not.³³ Animal data also suggest that medroxyprogesterone acetate may inhibit the beneficial effects of estrogen on endothelial-dependent vasodilation,³⁴ but this has not been documented in women.³⁵ Despite these mechanistic data suggesting an adverse effect of medroxyprogesterone acetate, observational studies show a similar reduction in CHD risk in women using medroxyprogesterone acetate plus estrogen as in women taking unopposed estrogen.⁴

Possible Differences in the Effects of Therapy Over Time

When the results were examined by year since randomization, the estrogen plus progestin regimen appeared to increase risk for primary CHD events in the first year of therapy but to decrease risk in subsequent years. This time trend

should be interpreted with caution. It could simply represent random variation, although the level of statistical significance makes this unlikely. More importantly, between-group contrasts that exclude the first several years are not true randomized comparisons, as the remaining study groups may no longer be comparable if, for example, treatment has caused high-risk individuals to have events early in the study.

On the other hand, the time trend is biologically plausible. The early increase in risk for CHD events might be attributable to an immediate prothrombotic, proarrhythmic, or proischemic effect of treatment that is gradually outweighed by a beneficial effect on the underlying progression of atherosclerosis, perhaps as a result of beneficial changes in lipoproteins. In trials of lipid interventions, the delay before CHD risk is reduced has ranged from 0 to 2 years.³⁶⁻⁴¹ After a lag period, the 11% net reduction in LDL cholesterol and 10% net increase in HDL cholesterol observed in the hormone group would be expected to reduce the risk of CHD events^{36,42} and may account for the trend toward a late benefit observed in HERS.

A pattern of early harm and later benefit could account for part of the discrepancy between the results of this trial and observational studies of estrogen and CHD. Attrition of susceptible individuals soon after starting estrogen replacement could increase the prevalence of survivors available for inclusion in observational studies; most observational studies are not designed to observe the

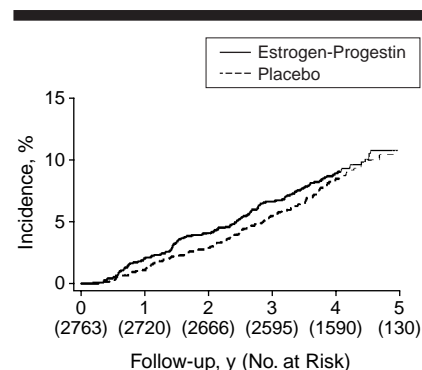


Figure 6.—Kaplan-Meier estimate of cumulative incidence of death from any cause. The number of women observed at each year of follow-up and still free of an event are provided in parentheses, and the curves become fainter when this number drops below half of the cohort. Log rank P value is .56.

onset of therapy or to detect an early adverse effect.

Previous Clinical Trial Evidence

The CHD data from previous hormone trials in women have been summarized⁴³ but are of limited value because the studies were small, short term, and not designed to examine CHD as an outcome. The only large prior trial of estrogen therapy to prevent CHD events was the Coronary Drug Project, which studied very high doses of estrogen (5.0 mg or 2.5 mg of conjugated equine estrogen daily) in men with preexisting CHD. The estrogen arms of this trial were stopped early because of an excess of MIs, thromboembolic events, and estrogenic symptoms in the 5.0-mg/d group⁴⁴ and the lack of benefit on the CHD end point and estrogenic symptoms in the 2.5-mg/d group.⁴⁵ The relevance of this trial of high-dose estrogen in men to postmenopausal hormone therapy in women is uncertain.

Safety and Other Noncardiovascular Outcomes

Venous thromboembolic events were 3 times more common in the hormone group than in the placebo group. Recent observational studies have reported similar relative risks for idiopathic venous thromboembolism among users of both unopposed estrogen⁴⁶⁻⁴⁹ and estrogen plus progestin therapy.^{47,49} The excess incidence of venous thrombotic events in HERS was 4.1 per 1000 woman-years of observation, an order of magnitude higher than the excess reported in the observational studies; the higher rate is probably a consequence of the facts that women enrolled in HERS were older and had multiple risk factors for venous thrombosis and that only idiopathic events were counted in the observational studies.

We found an increased risk of gallbladder disease in the hormone group that is

likely attributable to the estrogen therapy. Metabolic studies indicate that estrogen enhances hepatic lipoprotein uptake and inhibits bile acid synthesis, resulting in increased biliary cholesterol and cholelithiasis.⁵⁰

Observational studies have suggested that therapy with postmenopausal estrogen for 5 years or less is not associated with an increased risk of breast cancer but that longer duration of therapy might be associated with a small increase in risk.⁵¹ The HERS trial was not large enough and therapy did not continue for long enough to address this issue.

The incidence of fractures in the hormone group was only slightly lower than in the placebo group. Wide CIs around the fracture risk estimates reveal inadequate statistical power and do not exclude a reduction in risk of hip fracture of as much as 51% or a reduction in risk of other fracture of as much as 27%.

Strengths and Limitations of the Trial

The CHD risk factor profile of women enrolled in HERS is similar to that of a random sample of US women with probable heart disease, suggesting that the findings of HERS may be generalized to that population.⁵² However, HERS did not evaluate the effect of estrogen plus progestin therapy in women without CHD, and it is not known whether our findings apply to healthy women. It is also not known whether use of a different progestin or of estrogen alone would have been beneficial.

HERS exceeded the recruitment goal by 18%, carried out a successful randomization, collected objective, blindly adjudicated disease outcome data, and achieved 100% vital status ascertainment. Compliance with hormone treatment, while lower than projected, was sufficient to produce LDL and HDL cholesterol changes that compare favorably with previous studies.³¹ The 95% CIs for the effect of treatment assignment on primary CHD events (RH, 0.99; 95% CI, 0.80-1.22) make it unlikely that HERS missed a benefit of more than 20% for the overall 4.1-year period of observation. However, this statistic does not address the possible late benefit of treatment suggested by the time trend analysis, which is plausible based on the finding of a 1- to 2-year lag period observed in lipid trials³⁶⁻⁴¹; a longer study would be more definitive for investigating this possibility.

Future Directions

HERS is the first large trial of the effect of postmenopausal estrogen plus progestin therapy on risk for CHD events. The findings differ from those of observational studies and studies with surrogate outcomes, emphasizing the

importance of basing treatment policies on randomized controlled trials.⁵³ Other randomized trials of postmenopausal hormone therapy are likely to answer some of the questions raised by HERS. The Women's Health Initiative Randomized Trial⁵⁴ includes a group of women who have undergone hysterectomy and receive unopposed estrogen as well as women with intact uterus who receive the same estrogen plus progestin regimen used in HERS. Participants are not required to have CHD and are generally younger than the HERS cohort. The Women's Health Initiative Randomized Trial plans to enroll 27 500 women and to report the results in 2005 after 9 years of treatment. Further information will also emerge from HERS as we continue disease event surveillance.

Several interventions have been proven to reduce risk for CHD events in patients with coronary disease, including aspirin, β -blockers, lipid lowering, and smoking cessation.⁵⁵ The need for encouraging these interventions for women with coronary disease is illustrated by the facts that 90% of the HERS cohort had LDL cholesterol exceeding 2.59 mmol/L (100 mg/dL) at baseline and that only 32% were receiving β -blockers.

Conclusions

First, in the population studied in HERS, ie, postmenopausal women with established coronary disease and an average age of 66.7 years, daily use of conjugated equine estrogens and medroxyprogesterone acetate did not reduce the overall risk for MI and CHD death or any other cardiovascular outcome during an average of 4.1 years of follow-up. This therapy did increase the risk of venous thromboembolic events and gallbladder disease.

Second, we did not evaluate the cardiovascular effect of treatment with unopposed estrogen, commonly used in women who have had a hysterectomy, or other estrogen plus progestin formulations. We also did not study women without coronary disease.

Third, based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving hormone treatment to continue. Extended follow-up of the HERS cohort and additional randomized trials are needed to clarify the cardiovascular effects of postmenopausal hormone therapy.

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References

1. Bush TL. Noncontraceptive estrogen use and risk of cardiovascular disease: an overview and critique of the literature. In: Korenman SG, ed. *The Menopause: Biological and Clinical Consequences of Ovarian Failure: Evolution and Management*. Norwell, Mass: Serono Symposia; 1990:211-223.
2. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med*. 1991;20:47-63.
3. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;117:1016-1037.
4. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch Intern Med*. 1994;154:1333-1339.
5. Sidney S, Petitti DB, Quesenberry CP Jr. Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. *Ann Intern Med*. 1997;127:501-508.
6. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation*. 1987;75:1102-1109.
7. Sullivan JM, Vander Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease. *Arch Intern Med*. 1990;150:2557-2562.
8. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med*. 1991;151:75-78.
9. O'Brien JE, Peterson ED, Keeler GP, et al. Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions. *J Am Coll Cardiol*. 1996;28:1111-1118.
10. Newton KM, LaCroix AZ, McKnight B, et al. Estrogen replacement therapy and prognosis after first myocardial infarction. *Am J Epidemiol*. 1997;145:269-277.
11. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am J Cardiol*. 1997;79:847-850.
12. O'Keefe JH, Kim SC, Hall RR, Cochran VC, Lawhorn SL, McCallister BD. Estrogen replacement therapy after coronary angioplasty in women. *J Am Coll Cardiol*. 1997;29:1-5.
13. Cauley JA, Cummings SR, Black DM, Mascioli SR, Seeley DG. Prevalence and determinants of estrogen replacement therapy in elderly women. *Am J Obstet Gynecol*. 1990;163:1438-1444.
14. Barrett-Connor E. Postmenopausal estrogen and prevention bias. *Ann Intern Med*. 1991;115:455-456.
15. Petitti DB. Coronary heart disease and estrogen replacement therapy: can compliance bias explain the results of observational studies? *Ann Epidemiol*. 1994;4:115-118.
16. Grady D, Applegate W, Bush T, et al. Heart and Estrogen/progestin Replacement Study (HERS):

design, methods and baseline characteristics. *Control Clin Trials*. 1998;19:314-335.

17. Rautaharju PM, Calhoun HP, Chaitman BR. Novacode serial ECG classification system for clinical trials and epidemiological studies. *J Electrocardiol*. 1992;34(suppl):179-187.
18. Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley SB. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease. *JAMA*. 1997;277:1281-1286.
19. Lan KKG, DeMets DL, Halperin M. More flexible sequential and non-sequential designs in long-term clinical trials. *Commun Stat Theory Method*. 1984;13:2339-2353.
20. Grady D, Hulley SB, Furberg C. Venous thromboembolic events associated with hormone replacement therapy. *JAMA*. 1997;278:477.
21. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol*. 1996;143:971-978.
22. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med*. 1996;335:453-461.
23. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health*. 1998;19:55-72.
24. Falkeborn M, Persson I, Adami H, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br J Obstet Gynaecol*. 1992;99:821-828.
25. Thompson SG, Meade TW, Greenberg G. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J Epidemiol Community Health*. 1989;43:173-178.
26. Rosenberg L, Palmer JR, Shapiro S. A case-control study of myocardial infarction in relation to use of estrogen supplements. *Am J Epidemiol*. 1993;137:54-63.
27. Mann RD, Lis Y, Chukwujindu J, Chanter DO. A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women. *J Clin Epidemiol*. 1994;47:307-312.
28. Samaan SA, Crawford MH. Estrogen and cardiovascular function after menopause. *J Am Coll Cardiol*. 1995;26:1403-1410.
29. Guetta V, Cannon RO. Cardiovascular effects of estrogen and lipid-lowering therapies in postmenopausal women. *Circulation*. 1996;93:1928-1937.
30. Sarrel PM. How progestins compromise the cardioprotective effects of estrogens. *Menopause*. 1995;2:187-190.
31. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women [published correction appears in *JAMA*. 1995;274:1676]. *JAMA*. 1995;273:199-208.
32. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1997;17:217-221.
33. Adams MR, Kaplan JR, Manuck SB, et al. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys: lack of an effect of added progesterone. *Arteriosclerosis*. 1990;10:1051-1057.
34. Williams JK, Honoré EK, Washburn SA, Clarkson TB. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. *J Am Coll Cardiol*. 1994;24:1757-1761.
35. McCrohon JA, Adams MR, McCredie RJ, et al. Hormone replacement therapy is associated with improved arterial physiology in healthy postmenopausal women. *Clin Endocrinol*. 1996;45:435-441.
36. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results, II: the relationship of reduction in incidence

of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365-374.

37. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
38. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.
39. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279:1615-1622.
40. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med*. 1987;317:1237-1245.
41. Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. *N Engl J Med*. 1990;323:946-955.
42. Rosenenson RS, Tangney CC. Antiatherothrombotic properties of statins. *JAMA*. 1998;279:1643-1650.
43. Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ*. 1997;315:149-153.
44. Coronary Drug Project Research Group. The Coronary Drug Project: initial findings leading to modifications of its research protocol. *JAMA*. 1970;214:1303-1313.
45. Coronary Drug Project Research Group. Findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA*. 1973;226:652-657.
46. Jick H, Derby LE, Myers MW, Vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet*. 1996;348:981-983.
47. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet*. 1996;348:977-980.
48. Grodstein F, Stampfer MJ, Goldhaber SZ, et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet*. 1996;348:983-987.
49. Gutthann SP, Rodriguez LAG, Castellsague J, Oliart AD. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *BMJ*. 1997;314:796-800.
50. Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women. *J Clin Invest*. 1991;87:237-246.
51. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 1997;350:1047-1059.
52. Herrington D, Fong J, Sempos CT, et al. Comparison of the HERS cohort with women with coronary disease from the NHANES III. *Am Heart J*. 1998;136:115-124.
53. Rossouw JE. Estrogens for prevention of coronary heart disease: putting the brakes on the bandwagon. *Circulation*. 1996;94:2982-2985.
54. Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. *Control Clin Trials*. 1998;19:61-109.
55. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol*. 1996;28:1328-1428.