

Cardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy

Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II)

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THE HEART AND ESTROGEN/progestin Replacement Study (HERS) was a randomized, blinded, placebo-controlled trial of the effect of 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate daily on coronary heart disease (CHD) event risk among 2763 postmenopausal women with documented CHD.¹ Overall, during 4.1 years of follow-up, there were no significant differences between the hormone and placebo groups in the primary outcome of CHD events (nonfatal myocardial infarction [MI] plus CHD-related death) or in any secondary cardiovascular outcomes.²⁻⁵ However, post-hoc analyses showed a statistically significant time

See also pp 58 and 99.

Context The Heart and Estrogen/progestin Replacement Study (HERS) found no overall reduction in risk of coronary heart disease (CHD) events among postmenopausal women with CHD. However, in the hormone group, findings did suggest a higher risk of CHD events during the first year, and a decreased risk during years 3 to 5.

Objective To determine if the risk reduction observed in the later years of HERS persisted and resulted in an overall reduced risk of CHD events with additional years of follow-up.

Design and Setting Randomized, blinded, placebo-controlled trial of 4.1 years' duration (HERS) and subsequent unblinded follow-up for 2.7 years (HERS II) conducted at outpatient and community settings at 20 US clinical centers.

Participants A total of 2763 postmenopausal women with CHD and average age of 67 years at enrollment in HERS; 2321 women (93% of those surviving) consented to follow-up in HERS II.

Intervention Participants were randomly assigned to receive 0.625 mg/d of conjugated estrogens and 2.5 mg of medroxyprogesterone acetate (n=1380), or placebo (n=1383) during HERS; open-label hormone therapy was prescribed at personal physicians' discretion during HERS II. The proportions with at least 80% adherence to hormones declined from 81% (year 1) to 45% (year 6) in the hormone group, and increased from 0% (year 1) to 8% (year 6) in the placebo group.

Main Outcome Measures The primary outcome was nonfatal myocardial infarction and CHD death. Secondary cardiovascular events were coronary revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease.

Results There were no significant decreases in rates of primary CHD events or secondary cardiovascular events among women assigned to the hormone group compared with the placebo group in HERS, HERS II, or overall. The unadjusted relative hazard (RH) for CHD events in HERS was 0.99 (95% confidence interval [CI], 0.81-1.22); HERS II, 1.00 (95% CI, 0.77-1.29); and overall, 0.99 (0.84-1.17). The overall RHs were similar after adjustment for potential confounders and differential use of statins between treatment groups (RH, 0.97; 95% CI, 0.82-1.14), and in analyses restricted to women who were adherent to randomized treatment assignment (RH, 0.96; 95% CI, 0.77-1.19).

Conclusions Lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow-up. After 6.8 years, hormone therapy did not reduce risk of cardiovascular events in women with CHD. Postmenopausal hormone therapy should not be used to reduce risk for CHD events in women with CHD.

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trend, with more CHD events in the hormone group than in the placebo group during the first year of treatment, and fewer in years 3 to 5.² HERS investiga-

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tors speculated that early increased risk might be due to a prothrombotic, proarrhythmic, or proischemic effect of treatment that is gradually outweighed by a beneficial effect on the progression of underlying atherosclerosis mediated by the observed favorable changes in low- and high-density lipoprotein cholesterol.²

The apparent pattern of early increase and later decrease in CHD events led to the recommendation that women with CHD should not start treatment with hormones for the purpose of preventing CHD events, but that those who were already taking hormones could continue. Women enrolled in HERS tended to follow this advice. Many of those randomized to hormones during the trial continued with open-label treatment prescribed by their personal physicians and most randomized to placebo elected not to start hormones. This provided an opportunity to continue outcome surveillance for several years (designated as HERS II) while many women remained on the regimen to which they had been randomized.

This article presents cardiovascular outcomes during a total of 6.8 years of observation to examine whether longer-duration postmenopausal hormone therapy resulted in a reduced risk of CHD events among women with documented CHD. A companion article⁶ examines the effects of treatment on noncardiovascular outcomes.

METHODS

Study Participants

The design, methods, baseline findings,¹ and main outcomes² of HERS have been published. Participants were postmenopausal women younger than 80 years with no prior hysterectomy and a history of at least one of the following: MI, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery. Women were randomly assigned to 0.625 mg/d of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate or to identical placebo.

At the end of the trial, in August 1998, participants were informed of their treat-

ment assignment and the main trial results. Participants assigned to placebo were advised by HERS investigators not to start hormone therapy for the purpose of preventing CHD events, given the observation of an early increased risk and no overall cardiovascular benefit. Participants assigned to hormone therapy were advised that it might be appropriate to continue therapy because there was some evidence that CHD event risk was reduced during years 3 to 5 of follow-up. HERS investigators recommended that all participants make their decisions about postmenopausal hormone therapy with their personal physician.

Clinical sites obtained institutional review board approval for continued observation of the cohort. All surviving participants were asked to enroll in follow-up, and those who agreed signed a new informed consent document.

Baseline and Follow-up

At baseline in HERS, we obtained information on demographics, reproductive and health history, risk factors for CHD, quality of life, and medication use. Participants underwent physical examination including breast and pelvic examinations with Papanicolaou tests and endometrial evaluations, screening mammography, standardized 12-lead electrocardiograms (ECGs), and measurement of fasting lipoprotein cholesterol levels.¹

During HERS, participants visited the clinic every 4 months to receive study medication and for ascertainment of cardiovascular and other events, adverse effects, and study medication adherence. Annually and at the final HERS visit, which took place an average of 4 months before enrollment in HERS II, all baseline measures except demographics and health history were repeated. During HERS II, participants were telephoned at 4-month intervals and asked about cardiovascular and other outcomes using the same questions used during HERS visits. They were also asked about use of hormones, selective estrogen-receptor modulators, β -blockers, aspirin, and lipid-lowering medications.

Telephone contacts were comparable in the randomized groups. The proportion of the 12-month telephone calls in HERS II that were completed, expressed as a percentage of those alive, was 92% in women randomized to hormones and 92% in those randomized to placebo. The proportion of telephone calls that took place within a window of 2 weeks of the target date was 62% for the hormone group and 61% for the placebo group and 99.2% and 98.9% of surviving women were successfully contacted at the end of HERS II, respectively.

Outcomes

The primary outcomes of HERS and HERS II were CHD events (CHD death and nonfatal MI). A CHD death included documented fatal MI, sudden death within 1 hour of onset of symptoms, unobserved death that occurred out of the hospital in the absence of other known cause, and death due to coronary revascularization or congestive heart failure. The diagnosis of nonfatal MI was based on an algorithm that included ischemic symptoms, ECG abnormalities, and elevated cardiac enzyme levels.¹ Other adjudication criteria have been described.^{1,2} The only change in these criteria for HERS II was that we discontinued routine ECGs that had been collected at each annual visit in HERS. This meant that we were unable to detect silent MIs in HERS II, a change unlikely to affect findings since only 4% of the MIs in HERS were silent.⁷ Secondary cardiovascular outcomes included coronary artery bypass graft surgery, percutaneous coronary revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease.¹⁻⁴

Documentation of clinical events was identical to that required in HERS. When potential cardiovascular events were reported, hospital and other records (including admission and discharge summaries, ECGs, reports of relevant diagnostic tests, and next-of-kin and

physician descriptions for out-of-hospital deaths) were requested and independently reviewed by 2 physicians at the HERS coordinating center, who were unaware of randomized treatment assignment in HERS or open-label hormone use during HERS II. Classification of CHD events was based on the same criteria used in HERS and required consensus of the reviewers or a third physician to resolve discordant classifications.

In addition to questioning women or their next of kin about possible outcome events and deaths at the 4-month telephone contacts, we also searched the Social Security Death Index for notification of death for HERS participants who did not enroll in HERS II, and for those enrolled in HERS II who did not complete the final telephone contact. When a participant was listed as dead on the Social Security Death Index, we obtained the death certificate.

Hospital records and other information pertaining to each possible CHD event were collected with similar completeness in the 2 randomized groups. Among HERS II women with a first nonfatal MI, the proportion with complete information available on the 3 criteria (ECG, enzymes, and symptoms) was 98% in women originally randomized to hormones and 98% in those randomized to placebo.

Study Termination

HERS II follow-up was planned to continue for 4 years. Data were kept confidential and reviewed annually by a small data review committee. We planned to stop follow-up and send participants the results if conditional power to detect an overall benefit in the group originally randomized to hormones (compared with the placebo group) became very low. The decision to terminate HERS II follow-up was made at the second annual review, and the HERS executive committee subsequently agreed that no useful information was likely to result from continuing HERS II follow-up to the end of the fourth year. By the time all closeout visits were completed, average follow-up in HERS II was 2.7 years.

Statistical Analyses

All data were entered, edited, and analyzed at the HERS coordinating center at the University of California, San Francisco. We included all CHD events that occurred before January 1, 2001, and all have been fully adjudicated. Duration of observation was computed among women who remained alive until the end of HERS II. The primary analyses are intention-to-treat and compare the risk of CHD events during HERS, HERS II, and overall (HERS and HERS II) among women assigned to hormone therapy with corresponding risk among women assigned to placebo. These intention-to-treat analyses use an unadjusted Cox proportional hazards model for time to first CHD event and categorize women according to treatment assignment without regard to subsequent use of open-label hormone therapy. For analyses of nonfatal outcomes, participants were censored at the time of death, loss to follow-up, or at their HERS closeout visit if they did not enroll in HERS II. All HERS participants not known to be dead were assumed to be alive.

We repeated the overall and annual analyses adjusting for potential confounders. Predictor variables included in the models were treatment assignment, baseline values of the variables in TABLE 1 that independently predicted primary CHD events at $P < .20$ in a backward stepwise model, and use of statin drugs during follow-up.

The effect of treatment was also estimated in adjusted as-treated analyses in which women were censored 30 days after they became nonadherent to their originally assigned treatment. During HERS, nonadherence was defined as nonuse of study medication or use of open-label hormone therapy among women assigned to placebo (oral or transdermal estrogen or estrogen plus progestin) for 30 days or more. During HERS II, among women originally assigned to hormone therapy, nonadherence was defined as nonuse of open-label hormone therapy for 30 days or more. Among those assigned to placebo, nonadherence in HERS II was

defined as use of any open-label hormone therapy for 30 days or more.

RESULTS

Enrollment and Follow-up

Of the 2763 women enrolled in HERS, 2510 were alive at the time of enrollment in HERS II (1260 in the placebo group and 1250 in the hormone group). Of these, 2321 (93%) agreed to enroll in HERS II (1165 in the placebo group and 1156 in the hormone group) (FIGURE 1). At the end of HERS II, closeout telephone contacts were completed for 99% of surviving women in both the placebo and hormone groups. Of the 10 surviving women enrolled in HERS II without a closeout contact, 5 (all in the placebo group) were known to be alive at the end of follow-up. Vital status for the other 5 women was not known, but they were not listed as dead in the Social Security Death Index. Average duration of follow-up was 2.7 years in HERS II and 6.8 years overall.

Characteristics of the HERS and HERS II participants did not differ between treatment groups at the time of randomization in HERS (Table 1).

Use of Hormone Therapy

Among women randomly assigned to hormone treatment in HERS, the proportion reporting 80% or more adherence to hormones was 81% during year 1 and declined to 45% during year 6 of follow-up. Among women assigned to placebo, none reported taking open-label hormones during year 1 and 8% during year 6 (FIGURE 2). During HERS II, the majority (89%) of women taking hormones reported taking oral conjugated estrogens of 0.625 mg/d with 86% taking the HERS study medication (0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate). The proportion of women who reported taking either raloxifene or tamoxifen was 0% in both treatment groups during HERS, and 3% in the hormone group and 4% in the placebo group by the final year of HERS II.

CHD Outcomes

There were no differences between women originally assigned to the hor-

hormone and placebo groups in the rates of CHD events during HERS (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.81-1.22), HERS II (RH, 1.00; 95% CI, 0.77-1.29), or overall (RH, 0.99; 95% CI, 0.84-1.17; TABLE 2). Similarly, there were no significant differences between the randomized groups during HERS, HERS II, or overall for CHD death, nonfatal MI, or any of the other secondary cardiovascular outcomes except nonfatal ventricular arrhythmia. In HERS II and overall, women originally assigned to hormone therapy had a higher rate of nonfatal ventricular arrhythmia compared with those assigned to placebo (HERS II RH, 3.30; 95% CI, 1.08-10.1;

overall RH, 1.97; 95% CI, 1.10-3.53). During 6.8 years of follow-up, there were 132 CHD deaths in the hormone group and 122 in the placebo group (sudden death, 67 and 69; MI, 27 and 24; congestive heart failure, 23 and 22; revascularization, 7 and 2; and other CHD death, 8 and 5). There were no statistically significant differences between HERS and HERS II in the RHs for the effects of hormone therapy on any CHD event (Table 2).

Risk for CHD Events by Year of Use

During the fifth and sixth through eighth years of overall observation, RHs for CHD events among women ran-

domly assigned to hormone therapy were 1.09 (95% CI, 0.71-1.66) and 0.99 (95% CI, 0.73-1.35; TABLE 3). Overall, there was no trend toward lower RHs with longer duration of hormone therapy (continuous trend in log RH, $P = .18$). In data-driven post-hoc comparisons, there was weak evidence for heterogeneity in the year-specific RHs for treatment ($P = .09$). The RH for the first year (1.52; 95% CI, 1.01-2.29) differed from the RH for the subsequent years combined (0.92; 95% CI, 0.77-1.09; interaction $P = .03$).

Survival curves for primary CHD events (FIGURE 3) correspond to the findings in Table 2 and Table 3. The

Table 1. Baseline Characteristics of Heart and Estrogen/Progestin Replacement Study (HERS) and HERS II Participants*

Characteristic	HERS			HERS II		
	Hormone (n = 1380)	Placebo (n = 1383)	P Value	Hormone (n = 1156)	Placebo (n = 1165)	P Value
Demographics						
Age, mean (SD), y	67 (7)	67 (7)	.33	67 (7)	67 (7)	.13
White, %	88	90	.14	89	91	.13
Education, mean (SD), y	13 (3)	13 (3)	.84	13 (3)	13 (2)	.84
Coronary risk factors						
Current smoker, %	13	13	.84	12	12	.84
Diabetes and taking medication, %	19	18	.44	17	16	.80
Blood pressure, mean (SD), mm Hg						
Systolic	135 (19)	135 (19)	.88	135 (18)	134 (18)	.50
Diastolic	73 (10)	73 (10)	.90	73 (10)	73 (10)	.33
Cholesterol level, mean (SD), mg/dL†						
Low-density lipoprotein	145 (38)	145 (37)	.80	144 (38)	144 (37)	.96
High-density lipoprotein	50 (13)	50 (13)	.39	50 (13)	50 (13)	.51
Lipoprotein (a)	34 (32)	34 (33)	.90	33 (31)	33 (33)	.94
Time since last menstrual period, mean (SD), y	18 (8)	18 (8)	.32	18 (8)	18 (8)	.12
Body mass index, mean (SD), kg/m ²	29 (6)	29 (6)	.60	29 (5)	29 (5)	.94
Exercise >3 times per week, %‡	39	38	.72	40	39	.41
Any alcohol consumption, %	39	40	.62	40	41	.64
General health poor or fair, %	24	24	.93	20	22	.38
Creatinine level, mean (SD), mg/dL§	62 (19)	62 (20)	.38	56 (18)	56 (19)	.90
Estrogen use prior to randomization, %	24	23	.43	25	23	.27
Coronary heart disease manifestations, %						
Myocardial infarction	50	52	.51	50	51	.58
Percutaneous coronary revascularization	43	43	.69	45	42	.24
Coronary artery bypass graft surgery	41	41	.66	41	40	.46
Signs of congestive heart failure	13	12	.44	11	10	.47
Medication use, %						
Aspirin	79	79	.80	80	80	.91
β-Blockers	33	32	.84	33	33	.90
Statins	35	37	.22	36	39	.20
Angiotensin-converting enzyme inhibitors	17	18	.50	16	17	.36

*All values were measured at the randomization visit in 1993-1994.

†To convert to mmol/L, multiply by 0.0259.

‡Exercise defined as walking for 10 or more consecutive minutes or attending a cardiac rehabilitation session.

§To convert to μmol/L, multiply by 88.4.

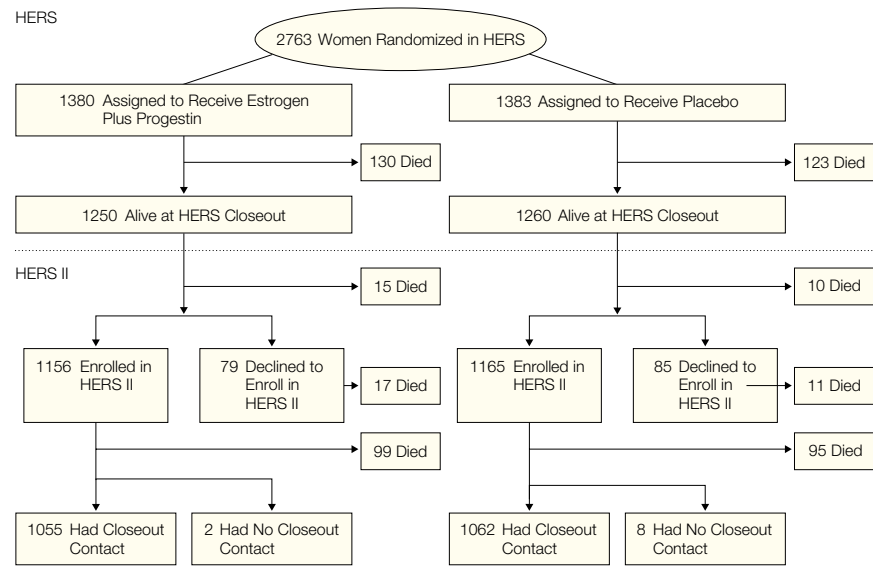
curves diverged during the early years of follow-up in HERS when the rate of CHD events was higher in the hormone than in the placebo-treated group. In the later years of HERS, the curves crossed as the rate of CHD events in the hormone group became lower than in the placebo group. During HERS II, the curves for each outcome were essentially parallel (overall log rank, $P = .97$).

Adjusted and per Protocol Analyses

There were no significant differences between the treatment groups during HERS in use of aspirin, β -blockers, angiotensin-converting enzyme inhibitors, or selective estrogen-receptor modulators. More women in the placebo group began treatment with lipid-lowering drugs, primarily statins, during follow-up. By enrollment in HERS II, 61% of women in the placebo group vs 54% in the hormone group reported statin use ($P < .001$). By the end of follow-up in HERS II, the proportion of statin use was 67% for the hormone group and 63% for the placebo group ($P = .01$). In secondary analyses, we adjusted for this difference by including statin use as a time-dependent covariate, and also for 15 potential baseline confounders listed in TABLE 4. The results of these adjusted analyses were similar to those obtained from the unadjusted intention-to-treat analyses (primary CHD events for HERS II, RH, 0.98; 95% CI, 0.75-1.22; and overall RH, 0.97; 95% CI, 0.82-1.14; Table 4). There were also no substantial differences in the unadjusted and adjusted RHs for CHD events in annual analyses. The results of these analyses were not changed when use of selective estrogen-receptor modulators was added to the adjusted models as a time-dependent covariate.

In secondary analyses, we adjusted for potential confounders and also limited the analyses to women who were 80% or more adherent to the regimen to which they were randomly assigned. In these as-treated analyses, the overall RH was 0.96 (95% CI, 0.77-1.19), closely resembling the unad-

Figure 1. Enrollment and Follow-up in HERS and HERS II

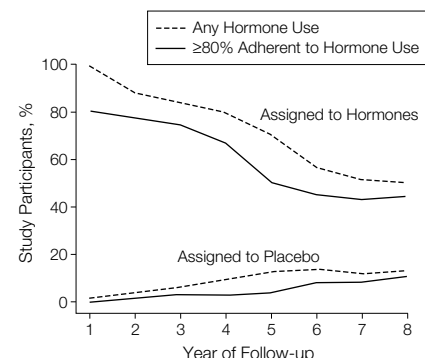


justed intention-to-treat estimate (Table 4). The as-treated RH for primary CHD events in HERS II was 0.82, somewhat lower than the unadjusted estimate of 1.00, and with a wider confidence interval (95% CI, 0.52-1.32) because there were fewer CHD events. The as-treated annual RHs varied substantially with no clear temporal pattern (continuous trend in log RH, $P = .09$). As-treated analyses should be viewed with caution because the treatment groups were not randomly assigned and only 73% of HERS and 37% of HERS II CHD events are included.

Effect of Hormone Therapy With Statin and Aspirin Use

We stratified our overall intention-to-treat analyses by statin or aspirin use during follow-up. For the entire 6.8 years of follow-up, the RH for CHD events comparing the hormone with the placebo group among women not taking statins was 1.12 (95% CI, 0.89-1.42), compared with 0.86 (95% CI, 0.69-1.08) for women taking statins. Among women taking aspirin, the RH was 1.01 (95% CI, 0.83-1.22) compared with 0.96 (95% CI, 0.70-1.31) among women not taking aspirin. None of the differences between the RHs for

Figure 2. Use of Hormones in HERS and HERS II Among Women Randomly Assigned to the Hormone and Placebo Groups



statin or aspirin use was significantly different and the results were similar in adjusted and as-treated analyses.

COMMENT

One of the most important questions at the end of the 4.1-year HERS trial was whether the lower rate of CHD events in the hormone group observed during the final years of the trial indicated that clear cardiovascular benefit would emerge with additional years of treatment. Data from this report do not support this hypothesis. Intention-to-treat analyses based on original

Table 2. Cardiovascular Events During Heart and Estrogen/Progestin Replacement Study (HERS), HERS II, and Overall

Outcome	Hormone		Placebo		Relative Hazard (95% Confidence Interval)*	P Value†	P Value‡
	No. of Events	Events/1000 Person-Years	No. of Events	Events/1000 Person-Years			
Primary Event							
CHD							
HERS	179	34.0	182	34.3	0.99 (0.81-1.22)	.94	.99
HERS II	111	41.8	111	42.1	1.00 (0.77-1.29)	.97	
Overall	290	36.6	293	36.8	0.99 (0.84-1.17)	.93	
CHD death							
HERS	70	12.7	59	10.6	1.20 (0.85-1.69)	.31	.46
HERS II	62	20.6	63	20.7	0.99 (0.70-1.41)	.96	
Overall	132	15.5	122	14.2	1.09 (0.85-1.39)	.49	
Nonfatal myocardial infarction							
HERS	122	23.2	134	25.2	0.92 (0.72-1.17)	.49	.76
HERS II	61	23.1	62	23.5	0.98 (0.69-1.40)	.91	
Overall	183	23.1	196	24.7	0.94 (0.77-1.15)	.54	
Secondary Event							
Coronary artery bypass graft surgery							
HERS	92	17.3	105	19.7	0.88 (0.66-1.16)	.36	.50
HERS II	52	19.4	50	18.8	1.04 (0.70-1.53)	.86	
Overall	144	18.0	155	19.4	0.93 (0.74-1.16)	.52	
Percutaneous coronary revascularization							
HERS	175	34.1	182	35.1	0.97 (0.79-1.19)	.77	.43
HERS II	80	32.4	71	28.7	1.13 (0.82-1.56)	.45	
Overall	255	33.5	253	33.0	1.02 (0.85-1.21)	.86	
Hospitalization for unstable angina							
HERS	109	20.6	120	22.7	0.91 (0.70-1.18)	.48	.47
HERS II	28	10.3	37	14.0	0.74 (0.45-1.21)	.23	
Overall	137	17.1	157	19.8	0.87 (0.69-1.09)	.23	
Ischemic event§							
HERS	374	77.8	388	81.0	0.96 (0.83-1.11)	.59	.85
HERS II	169	79.0	173	84.3	0.94 (0.76-1.16)	.56	
Overall	543	78.2	561	82.0	0.96 (0.85-1.07)	.44	
Hospitalization for congestive heart failure							
HERS	132	25.0	128	24.0	1.04 (0.82-1.33)	.74	.95
HERS II	45	16.6	43	15.6	1.06 (0.70-1.61)	.79	
Overall	177	22.2	171	21.1	1.05 (0.85-1.29)	.66	
Nonfatal ventricular arrhythmia							
HERS	20	3.7	13	2.3	1.56 (0.78-3.13)	.21	.27
HERS II	13	4.5	4	1.4	3.30 (1.08-10.1)	.04	
Overall	33	3.9	17	2.0	1.97 (1.10-3.53)	.02	
Sudden death							
HERS	31	5.6	31	5.6	1.01 (0.61-1.66)	.98	.88
HERS II	36	11.9	38	12.5	0.96 (0.61-1.51)	.85	
Overall	67	7.8	69	8.0	0.98 (0.70-1.37)	.90	
Stroke/transient ischemic attack							
HERS	112	20.9	103	19.2	1.09 (0.84-1.43)	.52	.99
HERS II	59	21.8	55	20.1	1.09 (0.75-1.57)	.65	
Overall	171	21.2	158	19.5	1.09 (0.88-1.35)	.44	
Peripheral arterial disease							
HERS	100	18.7	116	21.7	0.86 (0.66-1.13)	.28	.94
HERS II	54	20.1	61	23.0	0.88 (0.61-1.27)	.48	
Overall	154	19.2	177	22.2	0.87 (0.70-1.08)	.20	

*Relative hazard from Cox models with treatment group as the predictor and time to first event as the outcome.
 †For between group comparison.
 ‡For difference (interaction) between the relative hazard in HERS and HERS II.
 §Includes CHD-related death, nonfatal myocardial infarction, and hospitalization for unstable angina or coronary revascularization.

Table 3. Coronary Heart Disease (CHD) Events Since Randomization

Period	Hormone			Placebo			Relative Hazard (95% Confidence Interval)*	P Value†
	No. of Participants	No. of Events	Events/1000 Person-Years	No. of Participants	No. of Events	Events/1000 Person-Years		
Primary CHD Events‡								
Year								
1	1380	57	42.5	1383	38	28.0	1.52 (1.01-2.29)	.18
2	1303	47	36.9	1334	49	37.7	0.98 (0.66-1.46)	
3	1247	35	28.7	1269	42	33.9	0.85 (0.54-1.33)	
4	1196	25	21.4	1209	42	35.9	0.60 (0.36-0.98)	
5	1133	45	41.4	1122	41	38.1	1.09 (0.71-1.66)	
6-8	1043	81	44.3	1039	81	44.8	0.99 (0.73-1.35)	
CHD Death								
Year								
1	1380	17	12.4	1383	11	8.0	1.56 (0.73-3.32)	.17
2	1352	19	14.2	1368	13	9.6	1.48 (0.73-2.99)	
3	1323	18	13.8	1343	17	12.8	1.07 (0.55-2.08)	
4	1288	13	10.3	1307	14	10.9	0.94 (0.44-2.00)	
5	1235	20	16.7	1243	19	15.8	1.06 (0.56-1.98)	
6-8	1153	45	21.9	1162	48	23.2	0.94 (0.63-1.41)	
Nonfatal Myocardial Infarction								
Year								
1	1380	42	31.3	1383	29	21.3	1.47 (0.91-2.36)	.43
2	1303	33	25.9	1334	38	29.3	0.89 (0.56-1.41)	
3	1247	20	16.4	1269	29	23.4	0.70 (0.40-1.24)	
4	1196	15	12.8	1209	30	25.6	0.50 (0.27-0.93)	
5	1127	28	25.9	1120	23	21.4	1.21 (0.70-2.10)	
6-8	1038	45	24.6	1037	47	26.0	0.95 (0.63-1.43)	

*Relative hazard from Cox models with treatment group as the predictor and time to first event as the outcome.

†Test of continuous trend in log-relative hazard.

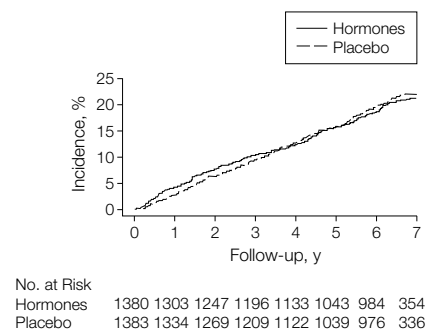
‡Includes nonfatal myocardial infarction and CHD death.

treatment assignment, analyses adjusted for differences in the 2 treatment groups that developed over time, and analyses restricted to women who continued their randomized treatment did not demonstrate any cardiovascular benefit during 6.8 years of observation.

In other trials of antiatherosclerotic interventions, including diet, niacin, and statin use, benefits observed during the first years of treatment persisted or increased over time, even in the absence of continued treatment.⁸⁻¹⁰ In 2.7 years of additional follow-up after HERS, we observed no cardiovascular benefit of randomized treatment with hormone therapy, despite the fact that about half of the women continued to take the originally assigned therapy.

Given the absence of overall long-term benefit of hormone therapy, there remain important questions about the pattern of CHD events over time in

HERS and HERS II. The RH for CHD events in the hormone group was higher in the first year of treatment and lower in the fourth year, but based on the entire 6.8 years of follow-up, there was no trend over time (continuous trend over time, $P = .18$). These results raise the possibility that the early increase in risk of CHD events observed in HERS, as well as the decrease in risk during years 3 to 5, may have occurred by chance. However, in this post-hoc analysis, the relative risk in the first year of hormone therapy is statistically higher than the average relative risk over the remainder of follow-up in the intention-to-treat analysis ($P = .03$). Other randomized trials have also reported an early increase in risk of CHD events related to postmenopausal hormone therapy.¹¹ Preliminary results from the Women's Health Initiative randomized trial of the effect of hormone therapy among 27347 women, few of

Figure 3. Kaplan-Meier Estimates of the Cumulative Incidence of CHD Events

Coronary heart disease (CHD) events are death and nonfatal myocardial infarction. The curves are truncated at year 7 when less than half of the cohort remains in follow-up.

whom had CHD at the start of the trial, revealed an increased risk of cardiovascular events during the first years of follow-up among women treated with either estrogen alone or estrogen plus

Table 4. Unadjusted, Adjusted, and As-Treated Values for Primary Coronary Heart Disease Events in Heart and Estrogen/Progestin Replacement Study (HERS), HERS II, and Overall

	Relative Hazard (95% Confidence Interval)		
	Unadjusted	Adjusted*	As Treated†
HERS	0.99 (0.81-1.22)	0.96 (0.78-1.18)	1.00 (0.78-1.27)
HERS II	1.00 (0.77-1.29)	0.98 (0.75-1.22)	0.82 (0.52-1.32)
Overall	0.99 (0.84-1.17)	0.97 (0.82-1.14)	0.96 (0.77-1.19)
Period, y			
1	1.52 (1.01-2.29)	1.51 (1.00-2.27)	1.52 (0.99-2.33)
2	0.98 (0.66-1.46)	0.94 (0.63-1.41)	1.00 (0.65-1.56)
3	0.85 (0.54-1.33)	0.80 (0.51-1.26)	0.57 (0.30-1.09)
4	0.60 (0.36-0.98)	0.56 (0.34-0.92)	0.58 (0.30-1.12)
5	1.09 (0.71-1.66)	1.06 (0.69-1.62)	1.32 (0.69-2.52)
6-8	0.99 (0.73-1.35)	0.98 (0.72-1.34)	0.71 (0.41-1.26)

*Adjusted for age, ethnicity, smoking, body mass index, diabetes, systolic blood pressure, creatinine clearance, exercise, general health, history of congestive heart failure and myocardial infarction, and baseline use of aspirin, angiotensin-converting enzyme inhibitors and statins, and statin use during follow-up.
†Estimates are adjusted for the variables listed above and are restricted to women who were adherent to therapy as defined in the "Methods" section.

a progestin.¹¹⁻¹³ The Coronary Drug Project secondary prevention trial found a similar pattern of early increase in nonfatal MI and CHD death in men randomized to a high dose of conjugated estrogens.¹⁴ Data from recent observational studies also suggest a possible early increase in risk of CHD events related to postmenopausal hormone therapy.^{15,16}

An early increased risk for CHD events might be due to prothrombotic, proinflammatory, or proarrhythmic effects of hormones.^{17,18} This risk may be limited to the first few years of therapy if tolerance to the risk develops, or if susceptible individuals experience CHD events and are removed from the at-risk cohort. We explored multiple subgroups in HERS to determine if certain women classified by age, prior manifestations of CHD, CHD risk factors, medication use, or other factors, might be particularly at risk for an early harm associated with hormone use. Among 86 subgroups evaluated for effect modification, there was no clear evidence that early risk was limited to specific subgroups.¹⁹ HERS substudies that are ongoing will attempt to address possible effect modification by proinflammatory and genetic factors, such as the prothrombin mutation associated with higher risk of CHD among hypertensive women taking estrogen.²⁰

We found an increased risk of nonfatal ventricular arrhythmia among women assigned to hormone therapy in HERS II and overall. Most of these events were ventricular arrhythmias that required resuscitation. The significance of this finding is unclear since there was no associated increased risk of sudden death, which is commonly due to ventricular arrhythmia in persons with CHD.

Our power to detect a persistent or increasing cardiovascular benefit was eroded by the progressively greater proportion of study participants who crossed over between the hormone and placebo groups. However, there was no convincing evidence of overall risk reduction in women who remained adherent to their randomized treatment assignment. The most appropriate measure of our power to detect a difference in risk of primary CHD events between the treatment groups after 6.8 years of follow-up is the precision of the adjusted overall RH for treatment of 0.97 (95% CI, 0.82-1.14). The CI demonstrates that it is highly unlikely that we missed a true reduction in CHD risk of 18% or greater.

The follow-up phase of HERS was unblinded, creating an opportunity for unintended interventions, biased outcome ascertainment, or biased outcome adjudication that could favor the placebo group. To minimize advice regard-

ing behaviors that might reduce CHD risk, such as diet and exercise, all HERS staff were instructed not to discuss CHD risk reduction during HERS II telephone contacts. There is no evidence that staff had more contact with either group, as telephone contacts occurred with similar frequency in the 2 treatment groups. Women in the placebo group were somewhat more likely to be prescribed lipid-lowering medication by their physicians in both HERS and HERS II, which we attribute to higher low-density lipoprotein cholesterol levels in the absence of estrogen treatment. In intention-to-treat analyses, adjustment for this difference had only a trivial effect on the findings. Biased outcome ascertainment is unlikely as follow-up was equally complete in the 2 treatment groups and documentation of outcome events was similar. Finally, biased outcome adjudication is unlikely, as outcome measures were objective and were adjudicated blindly using the same criteria in HERS and HERS II.

Randomized therapy in HERS consisted of 0.625 mg of oral conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate daily. The impact on CHD risk associated with other types and doses of estrogen, or with unopposed estrogen, remains uncertain. It has been suggested that the addition of medroxyprogesterone acetate to the conjugated estrogen used in HERS may have negated any cardiovascular benefit of estrogen. However, results of the Estrogen Replacement and Atherosclerosis trial suggest that unopposed estrogen is no more effective than estrogen plus medroxyprogesterone acetate.²¹ Findings in the Women's Estrogen for Stroke Trial,²² which compared unopposed oral estradiol with placebo, mirrored the HERS result of no overall benefit in either stroke or CHD outcomes.³ Thus, it seems unlikely that the addition of a progestin or the type of estrogen accounts for our findings.

Conclusions

HERS II was undertaken primarily to determine if the apparent decrease in risk of CHD observed in the later years

of the HERS trial persisted or became more marked resulting in overall benefit. Follow-up of the HERS cohort was extended to a total of almost 7 years. Despite the fact that almost half of the women originally assigned to hormone therapy were still taking hormones at the end of follow-up, there was no evidence of overall benefit for any cardiovascular outcome. Our findings lend additional support to recent recommendations that postmenopausal hormone therapy should not be used for the purpose of reducing risk for CHD events in women with CHD.²³

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Author Contributions: Dr Grady, as coprincipal investigator of HERS and HERS II, had full access to all of the data in the studies and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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Study supervision: Grady, Hulley, Herd, Khan, Wenger.

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Role of the Sponsor: Wyeth-Ayerst Research funded the study, contributed to its design, oversaw quality control at the clinical centers including periodic site visits, and edited the data collected by the clinical centers (except for disease outcome data) before sending it to the coordinating center at University of California, San Francisco. The sponsor did not have access to the blinding code, and played no role in collecting or adjudicating disease outcomes nor in data analysis. The sponsor had the opportunity to review and comment on manuscripts that had been written by the investigators, but our contract gave the investigators the final decision as to content.

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Comment. Very little US family medicine training occurs in rural areas. In the aggregate, 7.5% of family medicine training in the United States occurs in rural areas, although 22.3% of Americans live in rural places.⁹ Establishing rural family medicine training programs in rural areas is one strategy that contributes to the production of rural physicians,⁵ but it has not been widely adopted in the United States.

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CORRECTIONS

Incorrect Units and Wording: In the Original Contribution entitled "Pathogenesis of High-Altitude Pulmonary Edema: Inflammation Is Not an Etiologic Factor" published in the May 1, 2002, issue of THE JOURNAL (2002;287:2228-2235), there were incorrect units in Figures 2 and 3 and Table 2. The units of bronchoalveolar lavage red blood cells should have been $10^3/\text{mL}$ (Figures and Table), and those of total protein should have been mg/dL (Table). The last sentence under "Echocardiography" should have read "The jugular venous pressure was measured by inspection and added to ΔP to calculate the systolic PA pressure."

Numbers Reversed: In the Original Contribution entitled "Cardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II)" published in the July 3, 2002, issue of THE JOURNAL (2002;288:49-57), 2 numbers were reversed. On page 53, the fourth sentence in the "Adjusted and per Protocol Analyses" section should read "By the end of follow-up in HERS II, the proportion of statin use was 63% for the hormone group and 67% for the placebo group ($P=.01$)."

Incorrect Year and Wording: In the Medical News & Perspectives article entitled "Walking in Beauty at Sage Memorial Hospital" published in the July 3, 2002, issue of THE JOURNAL (2002;288:29-34), an incorrect year appeared on page 29 in the second sentence in the photo caption. It should read "Right, Louis A. Kazal, Jr, the hospital's medical director from 1996 to 1999, in front of a mural outside the old gymnasium, now the Wellness Center." On page 34, the second sentence in the "Volunteers Are Welcome" section should read "For example, Preston Manning, MD, a now retired Mayo Clinic-trained surgeon, 'helped out' for 2 years."

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