Noncardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy

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

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Context The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized trial of estrogen plus progestin therapy after menopause.

Objective To examine the effect of long-term postmenopausal hormone therapy on common noncardiovascular disease outcomes.

Design and Setting Randomized, blinded, placebo-controlled trial of 4.1 years' duration (HERS) and subsequent open-label observational follow-up for 2.7 years (HERS II), carried out between 1993 and 2000 in outpatient and community settings at 20 US clinical centers.

Participants A total of 2763 postmenopausal women with coronary disease 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 plus 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 Thromboembolic events, biliary tract surgery, cancer, fracture, and total mortality.

Results Comparing women assigned to hormone therapy with those assigned to placebo, the unadjusted intention-to-treat relative hazard (RH) for venous thromboembolism declined from 2.66 (95% confidence interval [CI], 1.41-5.04) during HERS to 1.40 (95% CI, 0.64-3.05) during HERS II (*P* for time trend=.08); it was 2.08 overall for the 6.8 years (95% CI, 1.28-3.40), and 3 of the 73 women with thromboembolism died within 30 days due to pulmonary embolism. The overall RH for biliary tract surgery was 1.48 (95% CI, 1.12-1.95); for any cancer, 1.19 (95% CI, 0.95-1.50); and for any fracture, 1.04 (95% CI, 0.87-1.25). There were 261 deaths among those assigned to hormone therapy and 239 among those assigned to placebo (RH, 1.10; 95% CI, 0.92-1.31). Adjusted and as-treated analyses did not alter our conclusions.

Conclusions Treatment for 6.8 years with estrogen plus progestin in older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery. Trends in other disease outcomes were not favorable and should be assessed in larger trials and in broader populations.

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THE HEART AND ESTROGEN/progestin Replacement Study (HERS) was a randomized, blinded trial to determine the effects of estrogen plus progestin compared with placebo in older postmenopausal women with coronary disease. Disease surveillance continued in HERS II for an additional 2.7 years, during which many of the women randomized to hormones took open-label estrogen prescribed by their personal physicians but only a few of those assigned to placebo did.[1] During the 6.8 years of observation in HERS and HERS II combined, we detected no overall effect of hormone therapy on cardiovascular disease (CVD) event rates.[1]

See also pp 49 and 99.

Author Affiliations and Financial Disclosures are listed at the end of this article.
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Hormone therapy after menopause can have effects on a variety of disease outcomes. We present data on non-CVD events over this extended period of hormone therapy. We examine whether the increase in risk of thromboembolic events observed in hormone-treated women in HERS[2] diminishes over time, as observational studies have suggested,[3,4] and whether the increased rate of biliary tract surgery that appeared to be present in hormone-treated women in HERS[5] is confirmed as additional events occur. More generally, we present data on the effect of hormone therapy on other disease outcomes thought to be associated with hormone therapy, including fractures, cancer, and total mortality.

METHODS

Study Participants and Baseline Measurements

The design and methods of HERS and HERS II have been described.[1,6,7] Briefly, participants were postmenopausal women younger than 80 years at baseline with coronary artery disease and no prior hysterectomy. Among the reasons for exclusion were a history of deep vein thrombosis or pulmonary embolism, history of breast cancer, endometrial hyperplasia or cancer, abnormal Papanicolaou (Pap) result, any hormone use within the past 3 months, and disease judged likely to be fatal within 4 years.

During the baseline period of HERS we obtained information by questionnaire and interview, and participants underwent physical examination, including pelvic examination with Pap smear and endometrial evaluation and screening mammography. All baseline measures except demographics and health history were repeated at the final HERS visit, an average of 4 months before enrollment in HERS II.

Treatment, Follow-up, and Outcomes

During the HERS trial, women were randomly allocated to receive either 0.625 mg/d of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate or an identical placebo. After stopping blinded medications at the end of the HERS trial, decisions about whether to undertake open-label hormone therapy were left to the women and their personal physicians. During HERS II participants were called at 4-month intervals and asked about hormone therapy and about symptoms or clinical encounters for possible disease events[1]; assessment of lipid-lowering drugs (but not bisphosphonates) was also continued during HERS II.

Disease events were ascertained and documented using the methods from the HERS trial.[7] For in-hospital nonfatal events and deaths, we required the hospital discharge summary and the following information: for pulmonary embolism, clinical signs or symptoms and a positive ventilation/perfusion scan or imaging result; for deep vein thrombosis, documentation by venography, impedance plethysmography, or Doppler ultrasound; for biliary tract surgery, an operative report; for clinical fracture, symptoms and a definite fracture on radiography; and for cancer, report of a tissue diagnosis. For all deaths in which clinical documentation was insufficient, we obtained a death certificate. For out-of-hospital deaths we interviewed the physician and/or next of kin for a description of the terminal event. Data pertaining to suspected outcome events were independently reviewed and classified according to the prespecified criteria used in the HERS trial by 2 physicians at the University of California, San Francisco Coordinating Center who were blinded to original treatment assignment and to open-label hormone therapy.[1,6,7]

Both the telephone contacts and the documentation of outcomes were carried out with similar efficiency and completeness in the 2 HERS randomized groups.[1] The proportions of all HERS II deaths for which we obtained clinical documentation beyond a death certificate were 81% among women originally randomized to hormone therapy and 82% among those randomized to placebo.

Statistical Analyses

As described,[1] the primary analyses (using SAS version 8.2, SAS Inc, Cary, NC) compared the risk of events among women assigned to hormone therapy with the risk among women assigned to placebo using unadjusted, intention-to-treat Cox proportional hazards models for time to first event. We censored women at the last contact or at loss to follow-up. In the analyses of biliary tract surgery, we excluded those with a cholecystectomy prior to enrollment in HERS.

Mortality was assessed in all HERS participants throughout the 6.8 years of follow-up, but morbidity surveillance during HERS II was limited to the 93% of surviving women who enrolled. To control for confounding, we estimated the effects of hormone therapy in adjusted Cox models that included all predictors significant at $P<.20$ in multivariate analysis. The 1993-1994 baseline values were used for all variables except statin use, which was included as a time-dependent covariate. In as-treated adjusted analyses, women were censored 30 days after they become nonadherent to randomly assigned treatment, defined as taking less than 80% of their HERS medication or its equivalent during HERS II.[1]

RESULTS

The number of women randomized in HERS was 1380 in the hormone therapy group and 1383 in the placebo group. Of these, 1156 and 1165 enrolled in HERS II, representing 93% of the 2485 surviving women. Vital status was known for 99.8% of these women at the end of HERS II, with final telephone contacts completed in 99.5% of known survivors (see Figure 1 on page 53). The mean duration of disease event surveillance was 6.8 years for women who survived, which included 2.7 years in HERS II.

Risk Factors and Other Characteristics

TABLE 1 presents risk factors for non-CVD outcomes using measurements made at the outset of HERS in 1993-1994. All the variables were equitably distributed between randomized groups for both the HERS and HERS II cohorts.

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Treatment With Hormones

Among women randomized to estrogen plus progestin, the proportions reporting at least 80% adherence to hormone therapy during years 1 through 6 were 81%, 78%, 74%, 67%, 50%, and 45%; comparable proportions for women randomized to placebo were 0%, 2%, 3%, 3%, 4%, and 8%.

Thromboembolism

There was a 2- to 3-fold increase in incidence of both deep vein thrombosis and pulmonary embolism in the hormone group during HERS (TABLE 2). The relative hazard (RH) for deep vein thrombosis was considerably smaller (1.23) and no longer statistically significant during HERS II. There was no comparable reduction in RH for pulmonary embolism, although the number of events available to detect such a time trend was small. When risk for venous thromboembolism was examined by year of observation (TABLE 3), the RH declined after the first 2 years, but the time trend was not statistically significant (P=.08).

The RH for any venous thromboembolic event over the entire 6.8 years was 2.08 (95% confidence interval [CI], 1.28-3.40). Event rates were 5.9 per 1000 person-years in the hormone group and 2.8 per 1000 person-years in the placebo group, an excess of 3.1 per 1000 person-years (P=.003). The number needed to treat (NNT) for 5 years per excess thromboembolic event is 65 when estimated by intention-to-treat and 50 in the as-treated analysis. Seven of the 73 women with thromboembolism died within 30 days of the event, and 3 of these deaths were judged due to the event (all were pulmonary embolisms in women randomized to hormone therapy). Stratifying the overall findings by baseline aspirin use, the data are weakly consistent with the hypothesis that aspirin attenuates the adverse effect of hormone therapy on risk of thromboembolism (RH, 1.68; 95% CI, 0.96-2.92 for aspirin users; RH, 4.23; 95% CI, 1.41-12.7 for nonusers; interaction P=.14).

Biliary Tract Surgery

The RH for biliary tract surgery in the hormone group compared with placebo was 1.39 during HERS, 1.70 during HERS II, and 1.48 overall (95% CI, 1.12-1.95) (Table 2). The overall RH after adjustment for statin use, a statistically significant predictor of lower rates of biliary tract surgery in our study, was 1.44 (95% CI, 1.10-1.90; P=.01).

The rate of surgery was 19.1 per 1000 person-years in the hormone group, an excess of 6.2 per 1000 person-years over the placebo group (P=.002). The estimated NNT for 5 years per excess surgery was 32 (intention-to-treat) and 31 (as-treated). Six of the 211 women who had biliary tract surgery died within 30 days, and 1 of these deaths was judged a consequence of the surgery.

Cancer

None of the differences between groups in cancer incidence was statistically significant (Table 2). The overall RH comparing the hormone and placebo groups was 1.27 (95% CI, 0.84-1.94) for the 88 breast cancer cases, 1.39 (95% CI, 0.84-2.28) for the 64 lung cancer cases, and 0.81 (95% CI, 0.46-1.45) for the 47 colon cancer cases. Death due to these cancers during the period of observation occurred in 3% of women with breast cancer, 61% of women with

Table 1. Characteristics of HERS Participants by Treatment Group*

	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 race, %	88	90	.14	89	91	.13
Education, mean (SD), y	13 (3)	13 (3)	.84	13 (3)	13 (2)	.84
Risk factors						
No. of children, mean (SD)	3 (2)	3 (2)	.76	3 (2)	3 (2)	.83
Age at first child's birth, mean (SD), y	23 (5)	23 (5)	.67	23 (5)	23 (5)	.87
Age at last menstrual period, mean (SD), y	49 (5)	49 (5)	.77	49 (5)	49 (5)	.64
Have first-degree relative with breast cancer, %	12	11	.58	12	12	.90
Current smoker, %	13	13	.84	12	12	.84
Body mass index, mean (SD), kg/m^2	29 (6)	29 (6)	.60	29 (5)	29 (5)	.94
Exercise >3 times weekly, %	39	38	.72	40	39	.41
Events prior to examination, %						
Fractures since menopause	22	22	.90	22	23	.70
Cholecystectomy	22	23	.49	22	24	.32
Medication use, %						
Estrogens (past use)	24	23	.43	25	23	.27
Statins	35	37	.22	36	39	.20
Fibrates	6	6	.77	6	6	.83
Aspirin	79	79	.80	80	80	.91
Bisphosphonates	<1	<1		<1	<1	

*All values were measured at the randomization visit in 1994. HERS indicates Heart and Estrogen/progestin Replacement Study.

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Table 2. Fatal and Nonfatal Noncardiovascular Events, by Treatment Group*

Outcomes	Hormone No.	Hormone Events per 1000 Person-years	Placebo No.	Placebo Events per 1000 Person-years	Relative Hazard (95% CI)	*P* Value for Each Time Period	*P* Value for Treatment-Time Interaction†
Deep vein thrombosis							
HERS	25	4.6	9	1.6	2.82 (1.32-6.04)	.008	.15
HERS II	12	4.2	10	3.4	1.23 (0.53-2.85)	.63	
Total	37	4.5	19	2.2	1.98 (1.14-3.45)	.02	
Pulmonary embolism							
HERS	11	2.0	4	0.7	2.78 (0.89-8.74)	.08	.93
HERS II	6	2.1	2	0.7	3.03 (0.61-15.0)	.18	
Total	17	2.0	6	0.7	2.86 (1.13-7.26)	.03	
Total thromboembolic events							
HERS	34	6.2	13	2.3	2.66 (1.41-5.04)	.003	.21
HERS II	15	5.3	11	3.8	1.40 (0.64-3.05)	.40	
Total	49	5.9	24	2.8	2.08 (1.28-3.40)	.003	
Biliary tract surgery							
HERS	85	19.7	62	14.2	1.39 (1.00-1.93)	.05	.51
HERS II	40	18.0	24	10.6	1.70 (1.03-2.83)	.04	
Total	125	19.1	86	12.9	1.48 (1.12-1.95)	.005	
Breast cancer							
HERS	34	6.2	25	4.5	1.38 (0.82-2.31)	.22	.59
HERS II	15	5.3	14	4.9	1.08 (0.52-2.24)	.83	
Total	49	5.9	39	4.7	1.27 (0.84-1.94)	.26	
Colon cancer							
HERS	11	2.0	16	2.9	0.69 (0.32-1.49)	.35	.52
HERS II	10	3.4	10	3.4	1.01 (0.42-2.43)	.98	
Total	21	2.5	26	3.1	0.81 (0.46-1.45)	.48	
Lung cancer							
HERS	24	4.4	19	3.4	1.28 (0.70-2.33)	.43	.64
HERS II	13	4.4	8	2.7	1.64 (0.68-3.96)	.27	
Total	37	4.4	27	3.2	1.39 (0.84-2.28)	.20	
Endometrial cancer							
HERS	2	0.4	5	0.9	0.39 (0.08-2.02)	.26	.99
HERS II	0	0.0	3	1.0	NA	NA	
Total	2	0.2	8	0.9	0.25 (0.05-1.18)	.08	
Other cancers							
HERS	32	5.8	31	5.6	1.04 (0.64-1.71)	.87	.16
HERS II	23	7.8	12	4.0	1.93 (0.96-3.89)	.06	
Total	55	6.5	43	5.1	1.29 (0.87-1.92)	.21	
Any cancer							
HERS	101	18.9	91	16.8	1.13 (0.85-1.49)	.42	.49
HERS II	58	21.4	44	16.0	1.34 (0.90-1.98)	.15	
Total	159	19.7	135	16.5	1.19 (0.95-1.50)	.13	
Hip fracture							
HERS	15	2.7	13	2.3	1.16 (0.55-2.44)	.69	.25
HERS II	25	8.7	12	4.1	2.11 (1.06-4.19)	.03	
Total	40	4.8	25	3.0	1.61 (0.98-2.66)	.06	
Wrist fracture							
HERS	29	5.3	29	5.3	1.01 (0.60-1.68)	.98	.88
HERS II	13	4.4	14	4.7	0.94 (0.44-1.99)	.86	
Total	42	5.0	43	5.1	0.98 (0.64-1.50)	.94	
Vertebral fracture							
HERS	14	2.5	19	3.4	0.74 (0.37-1.48)	.40	.47
HERS II	12	4.0	11	3.7	1.10 (0.49-2.50)	.81	
Total	26	3.1	30	3.5	0.87 (0.52-1.48)	.62	
Other fracture							
HERS	91	17.1	101	18.8	0.91 (0.69-1.21)	.52	.71
HERS II	53	19.2	53	19.3	1.00 (0.68-1.46)	.99	
Total	144	17.8	154	18.9	0.94 (0.75-1.18)	.60	
Any fracture							
HERS	140	26.7	148	28.0	0.96 (0.76-1.20)	.70	.22
HERS II	90	35.7	74	29.4	1.22 (0.89-1.65)	.22	
Total	230	29.7	222	28.4	1.04 (0.87-1.25)	.66	

*CI indicates confidence interval; NA, not applicable.

†For difference (interaction) between the relative hazard in HERS and HERS II.

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lung cancer, and 17% of women with colon cancer.

Other cancers that occurred in at least 5 women included endometrial cancer (2 women in the hormone group and 8 in placebo); malignant melanoma (3 hormone and 5 placebo); lymphoma (7 hormone and 1 placebo); and ovarian cancer (5 hormone and 2 placebo). The total number of women with any cancer was 159 in the hormone group vs 135 in the placebo group (RH, 1.19; 95% CI, 0.95-1.50).

Fractures

Women randomized to hormone therapy had more hip fractures than women randomized to placebo; the overall RH during 6.8 years of observation was 1.61 (95% CI, 0.98-2.66; $P = .06$) (Table 2). The RH was 1.16 in HERS and 2.11 in HERS II, a difference that is not statistically significant.

The RH estimates for vertebral, wrist, and other fractures were close to unity. Based on the total of 452 clinical fractures during 6.8 years of observation, the RH for any fracture was 1.04 (95% CI, 0.87-1.25). Prevalence of bisphosphonate use was 2.6% at HERS closeout (in 1998) among women randomized to hormone therapy and 2.5% among those randomized to placebo.

Mortality

Death rates were high and increasing in this population of older women with coronary disease. Total mortality in the placebo group was 22 per 1000 person-years during HERS and 38 per 1000 person-years during HERS II (TABLE 4). The RH for total mortality in the hormone vs placebo group was 1.06 during HERS, 1.14 during HERS II, and 1.10 overall (95% CI, 0.92-1.31).

During the entire 6.8 years of observation, there were 261 deaths in the hormone group and 239 in the placebo group. Overall, 61% of the deaths were classified as due to CVD, 19% due to cancer, and 20% due to other cause. Among the CVD deaths, 132 women in the hormone group and 122 in the placebo group died of CHD and the remainder died of stroke (23 and 20) and peripheral arterial disease (4 and 2). Among the cancer deaths, 3 were due to breast cancer (all in women randomized to hormone therapy). For lung cancer deaths 20 occurred in women randomized to hormone therapy and 19 in those randomized to placebo; for colon cancer deaths, 2 and 6; and for all other cancer deaths, 26 and 19. Among the non-CVD noncancer deaths, the numbers in the hormone and placebo groups were 24 and 14 for infectious diseases (including pneumonia and all forms of sepsis); 15 and 13 for respiratory failure (primarily chronic obstructive pulmonary disease, exclud-

Table 3. Venous Thromboembolic Events by Treatment Group and Year Since Randomization*

Year Since Randomization	Hormone No.	Hormone Events per 1000 Person-years	Placebo No.	Placebo Events per 1000 Person-years	Relative Hazard (95% CI)†
1	13	9.6	4	2.9	3.28 (1.07-10.1)
2	8	6.1	2	1.5	4.09 (0.87-19.3)
3	7	5.5	3	2.3	2.39 (0.62-9.26)
4	6	4.9	3	2.4	2.05 (0.51-8.21)
5	4	3.5	4	3.4	1.02 (0.26-4.09)
6-7	11	5.5	8	3.9	1.40 (0.57-3.49)

*CI indicates confidence interval.
†Relative hazard from Cox models with treatment group as the predictor and time to first event as the outcome. For tests of continuous trend over time in log-relative hazard, $P = .08$.

Table 4. Deaths by Treatment Group*

Outcomes	Hormone No.	Hormone Events per 1000 Person-years	Placebo No.	Placebo Events per 1000 Person-years	Relative Hazard (95% CI)	*P* Value for Each Time Period	*P* Value for Treatment-Time Interaction†
CVD death							
HERS	88	15.9	70	12.6	1.27 (0.93-1.73)	.14	.24
HERS II	71	23.5	74	24.3	0.97 (0.70-1.34)	.84	
Total	159	18.6	144	16.7	1.11 (0.89-1.39)	.36	
Cancer death							
HERS	21	3.8	24	4.3	0.88 (0.49-1.58)	.67	.19
HERS II	30	10.0	20	6.6	1.51 (0.86-2.66)	.15	
Total	51	6.0	44	5.1	1.17 (0.78-1.75)	.45	
Non-CVD, noncancer death							
HERS	21	3.8	29	5.2	0.73 (0.42-1.28)	.27	.11
HERS II	30	10.0	22	7.2	1.38 (0.79-2.38)	.26	
Total	51	6.0	51	5.9	1.01 (0.68-1.49)	.97	
Any death							
HERS	130	23.5	123	22.1	1.06 (0.83-1.36)	.62	.71
HERS II	131	43.4	116	38.1	1.14 (0.89-1.46)	.31	
Total	261	30.6	239	27.8	1.10 (0.92-1.31)	.29	

*CI indicates confidence interval; CVD, cardiovascular disease.
†For difference (interaction) between the relative hazard in HERS and HERS II.

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ing pneumonia); 2 and 9 for traumatic causes, and 10 and 15 for all other causes.

Adjusted and As-Treated Analyses

In addition to the unadjusted intention-to-treat findings described above, we also estimated the effects of hormone therapy in Cox regression analyses that adjusted for covariates that were predictors of the outcome. The purpose was to adjust for imbalances that could have developed because some women declined to enroll in HERS II. None of the RH estimates was appreciably altered by the multivariate adjustment (TABLE 5).

We also carried out analyses restricted to women who remained adherent to randomly assigned treatment (Table 5). These as-treated RH estimates had wider CIs than the intention-to-treat estimates due to the smaller numbers of events (40%-73% of the total in the various models). The as-treated RH for venous thromboembolism was higher than the unadjusted intention-to-treat value (3.04 vs 2.08 for the overall study); the as-treated RH was 5.83 during HERS (95% CI, 2.23-15.3) and 0.70 during HERS II (95% CI, 0.14-3.64). Other as-treated RH estimates in Table 5 differed somewhat from those estimated by intention-to-treat, but the CIs largely overlapped.

COMMENT

This report examines non-CVD outcomes over a total of 6.8 years of observation during and following the HERS randomized trial of hormone therapy in postmenopausal women with coronary disease. We found an increased risk of venous thromboembolism and biliary tract surgery among women randomized to hormone therapy; rates of other important disease outcomes were not favorably affected.

Deep Vein Thrombosis and Pulmonary Embolism

HERS[2,7] confirmed reports from observational studies[3,8,9] that hormone therapy after menopause increases risk of venous thromboembolism. The estrogen component of HERS treatment is the likely cause because estrogen without progestin is associated with venous thromboembolism[3,4] and selective estrogen receptor modulators also increase the risk.[10,11] Risk factors for thromboembolism in HERS participants included lower extremity fracture, cancer, surgery, and nonsurgical hospitalization; use of aspirin or statins appeared to be protective.[2]

HERS participants represent a population at relatively high absolute risk of deep vein thrombosis or pulmonary embolism. The overall rate in the placebo group, 2.8 per 1000 person-years, is far higher than that observed in healthy young postmenopausal women but resembles rates in other populations of elderly women.[3,12] Therefore our estimated NNT, 1 excess thromboembolic event among every 50 to 65 women taking hormones for 5 years, is probably much smaller than it would be for younger and healthier women.

The longer follow-up available in HERS II suggests that the relative risk for venous thromboembolic events may decrease after the second year of hormone therapy ($P = .08$). Similar decreases over time have been reported in observational studies of postmenopausal hormone[3,4] and oral contraceptive[13] use, although there is generally some residual excess risk. A decreasing risk is plausible, either through attrition of a susceptible subgroup[14] or by developing tolerance, and the as-treated analysis suggests that it is not just due to decreased compliance with hormone therapy during HERS II. However, the decrease might partly reflect our decision in 1997 (after noting that venous thromboembolism was more common in hormone-treated women)

Table 5. Overall Relative Hazards of Main Outcomes Comparing Women Randomized to Hormone Therapy With Those Randomized to Placebo*

	Hazard Estimate (95% CI)		
	Unadjusted Intention-to-Treat	Adjusted Intention-to-Treat†	Adjusted As-Treated‡
Venous thromboembolism	2.08 (1.28-3.39)	2.06 (1.26-3.36)	3.04 (1.46-6.31)
Biliary tract surgery	1.48 (1.12-1.95)	1.44 (1.10-1.90)	1.35 (0.94-1.93)
Cancer			
Breast	1.27 (0.84-1.94)	1.27 (0.84-1.94)	1.11 (0.61-2.03)
Lung	1.39 (0.84-2.28)	1.43 (0.87-2.37)	1.73 (0.93-3.21)
Colon	0.81 (0.46-1.45)	0.82 (0.46-1.47)	0.58 (0.25-1.35)
Any	1.19 (0.95-1.50)	1.19 (0.95-1.50)	1.24 (0.91-1.68)
Fracture			
Hip	1.61 (0.98-2.66)	1.61 (0.97-2.66)	1.18 (0.54-2.58)
Wrist	0.98 (0.64-1.50)	1.00 (0.65-1.53)	0.90 (0.54-1.49)
Spine	0.87 (0.52-1.48)	0.89 (0.53-1.50)	0.80 (0.36-1.77)
Any	1.04 (0.87-1.25)	1.07 (0.89-1.29)	0.97 (0.76-1.23)
Total mortality	1.10 (0.92-1.31)	1.08 (0.91-1.29)	1.11 (0.84-1.47)

*CI indicates confidence interval.

†Adjusted models are adjusted for age and for predictors of the outcome in a multivariate model at $P<.20$ (adjusted treatment effects are similar in larger models that include additional covariates); all covariates are those measured at randomization except statins, which are current use. The covariates used in adjusting each model were as follows. *Venous thromboembolism:* age, age at last menstrual period, systolic blood pressure, and statin use. *Biliary tract surgery:* age, alcoholic drinks per week, body mass index (BMI), high-density lipoprotein cholesterol, coronary surgery, prior gallbladder disease, and hypertension. *Breast cancer:* age, number of pregnancies, age at first pregnancy, first-degree relative with breast cancer, and BMI. *Lung cancer:* age, education, current and former smoking, BMI, low-density lipoprotein cholesterol, and digitalis use. *Colon cancer:* age, smoking, diastolic blood pressure, low-density lipoprotein cholesterol, and β-blocker use. *Any cancer:* age, current or former smoker, any alcohol use, waist-hip ratio, hypertension, baseline use of aspirin or β-blockers, and first-degree relative with breast cancer. *Wrist fracture:* age, smoking, BMI, waist-hip ratio, history of postmenopausal fracture, Lp(a) lipoprotein, and aspirin use. *Spine fracture:* age, nonwhite race, BMI, creatinine clearance <40 mL/min, history of postmenopausal fracture, and digitalis use. *Hip fracture and any fracture:* age, diuretic use, statin use, history of fracture, and exercise. *Total mortality:* age, nonwhite race, current smoker, waist-hip ratio, diabetes, creatinine clearance <40 mL/min, uric acid, poor/fair self-reported health, hypertension, congestive heart failure, coronary artery surgery, statin use, and baseline use of digitalis or diuretics.

‡As-treated analyses were restricted to women who remained adherent to randomly assigned treatment and thus included 51% of thromboembolic events; 59% of biliary tract operations; 49% of breast cancers; 66% of lung cancers; 53% of colon cancers; 56% of any cancers; 40% of hip fractures; 73% of wrist fractures; 48% of spine fractures; 61% of any fractures; and 41% of the deaths.

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to emphasize to study participants the need to stop HERS treatment in the event of fracture, immobilization, surgery, or cancer.[15]

Biliary Tract Surgery

Several decades ago the Coronary Drug Project randomized trial found that high-dose estrogen therapy caused gallbladder disease in men,[16] probably due to alteration of the concentration of cholesterol in the bile,[17] and observational studies of women receiving postmenopausal estrogen have had similar findings.[5] We previously reported a 38% higher adjusted rate of biliary tract surgery in hormone-treated women (P=.09).[5] The longer period of observation reported here has revealed the increased risk to be statistically significant. Gallbladder disease was 3 times more common than venous thromboembolism in HERS women, and the NNT for 5 years to cause 1 excess surgery was 31.

Cancer

Cancer was 19% more common in the hormone therapy group, but the finding was not statistically significant, nor were there statistically significant differences in the rates of any specific cancer. The most common of these, breast cancer, occurred slightly more frequently in the hormone group; the second most common, lung cancer, also occurred slightly more frequently in the hormone group; and the third most common, colon cancer, occurred slightly less often in the hormone group. For each of these 3 cancers, statistically significant associations in the same direction have been found in observational studies and biological plausibility has been discussed.[18-23] However, the wide CIs and limited duration of follow-up do not permit clear inferences from these observations of cancer occurrence.

Risk of endometrial cancer was 75% lower among women randomized to hormone therapy than among those assigned to placebo, but the difference was not statistically significant. The fact that risk is not increased provides assurance that the progestin component of HERS treatment prevents the endometrial hyperplasia and cancer resulting from prolonged use of estrogen.[24,25]

Fracture

Estrogen is widely believed to prevent osteoporotic fractures. Observational studies reveal 50% lower fracture rates among women taking hormones than in women who are not,[26,27] and there is strong clinical trial evidence for a favorable effect of postmenopausal estrogen treatment, with or without progestin, on bone mineral density in various populations, including older women.[28,29] However, the clinical trial evidence for an effect on fractures has been limited.[30,31] Our earlier report from the HERS main trial revealed little difference between the hormone and placebo groups in risk of any type of fracture.[32] Surprisingly, the additional follow-up experience from HERS II suggests a risk of hip fracture among women in the hormone therapy group that is higher than that in the placebo group. Chance may explain the finding, which does not meet the criteria for statistical significance, is considerably smaller in the as-treated analysis, and lacks biological plausibility.

Chance also could play a role in the larger question as to why we did not observe any reduction in risk of all fractures in the hormone group, although the confidence interval makes it unlikely that we missed a large benefit. The absence of routine spine radiographs limited our ability to detect vertebral fractures. Women studied in HERS were not selected for osteoporosis and are therefore not well suited to revealing the effects of fracture-prevention treatments. Clinical trials of bisphosphonates have found an effect on the risk of fracture in women with osteoporosis, but not in women with normal bone density.[33,34]

Mortality

We recorded 261 deaths in the hormone group and 239 in the placebo group. The absence of mortality benefit contrasts with the finding in observational studies of lower mortality rates among women who use postmenopausal hormones compared with nonusers.[35,36] Population differences could underlie this disparity, but we believe that the lower mortality rate among hormone users in observational studies is primarily due to confounding; women who seek hormone therapy and remain compliant tend to be healthier and wealthier than those who do not.[37-39] Because these characteristics cannot be measured precisely, their influence cannot be adequately addressed by statistical adjustment in observational studies.[40]

Strengths and Limitations

Clinical trials have shown that short-term hormone therapy after menopause has favorable effects on surrogate markers for disease, such as blood lipid levels and bone mineral density, and that it relieves menopausal symptoms such as hot flushes and insomnia,[41,42] but the effects of prolonged hormone therapy in preventing clinical events have not been established. HERS is the first randomized trial to provide substantial information on the common disease outcomes that hormones may influence.

HERS II increases the precision of the estimated RHs by adding events that reflect carryover effects from the randomized treatment phase as well as the effects of continuation of the originally assigned treatment. About 50% of the hormone group used open-label treatment during HERS II compared with less than 10% of the placebo group. Those women who did not continue their randomly assigned treatment (crossovers) diminish the power to observe effects of the randomized treatment but do not alter the fundamental value of randomization. To take advantage of this value, our primary analytic approach was an intention-to-treat comparison of outcomes measured over the entire 6.8 years. However, we also examined the findings with as-treated analyses to compensate for the effects of crossing over and with adjusted analyses to compensate for base-

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line differences resulting from the 7% of women who did not enroll in HERS II. The as-treated and adjusted findings differ somewhat from those of intention-to-treat, but the overall conclusions are not altered.

Inferences about the effects of randomized treatments are also contingent on avoiding unintended interventions applied disproportionately to one randomized group. Randomized assignment was no longer blinded in HERS II, so at the HERS closeout visit and in subsequent telephone calls we provided a neutral message to all women and left advice on hormone use and other preventive treatments to their personal physicians. We also took steps to prevent bias in the ascertainment of outcomes by choosing disease events that were objective and by maintaining the HERS systems for obtaining records and for blinded adjudication. The success of efforts to avoid between-group bias is supported by the comparability in the timing and completeness with which the telephone contacts were made and clinical event data collected.[1]

Important limitations of HERS stem from the older age of HERS participants, who averaged 67 years at baseline and 74 years at the end of HERS II, the presence of coronary disease on entry, and the particular estrogen and progestin that we chose to study. These characteristics limit generalizability, and the effects of other hormones in younger, healthier postmenopausal women may be different. Further information on the effects of hormone therapy on disease outcomes in healthy postmenopausal women will be available at the conclusion of the Women's Health Initiative randomized trial.[43]

CONCLUSIONS

Treatment with estrogen plus progestin in older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery and did not produce favorable trends in overall rates of CVD,[1] fracture, or death. Postmenopausal hormone therapy should be limited to indications that are supported by randomized trial evidence that beneficial clinical outcomes outweigh harmful ones.

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