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Heart and Estrogen/progestin Replacement Study (HERS): Design, Methods, and Baseline Characteristics

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ABSTRACT: The Heart and Estrogen/progestin Replacement Study (HERS) is a randomized, double-blind, placebo-controlled trial designed to test the efficacy and safety of estrogen plus progestin therapy for prevention of recurrent coronary heart disease (CHD) events in women. The participants are postmenopausal women with a uterus and with CHD as evidenced by prior myocardial infarction, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or other mechanical revascularization or at least 50% occlusion of a major coronary artery.

Between February 1993 and September 1994, 20 HERS centers recruited and randomized 2763 women. Participants ranged in age from 44 to 79 years, with a mean age of 66.7 (SD 6.7) years. Most participants were white (89%), married (57%), and had completed high school or some college (80%). As expected, the prevalence of coronary risk factors was high: 62% were past or current smokers, 59% had hypertension, 90% had serum LDL-cholesterol of 100mg/dL or higher, and 23% had diabetes.

Each woman was randomly assigned to receive one tablet containing 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate daily or an identical placebo. Participants will be evaluated every 4 months for an average of 4.2 years for the occurrence of CHD events (CHD death and nonfatal myocardial infarction). We will also assess other major CHD endpoints, including revascularization and hospitalization for unstable angina. The primary analysis will compare the rate of CHD events in women assigned to active treatment with the rate in those assigned to placebo. The trial was designed to have power greater than 90% to detect a 35% reduction in the incidence of CHD events, assuming a 50% lag in effect for 2 years and a 5% annual event rate in the placebo group.

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The design, analysis, and conduct of the study are controlled by the Steering Committee of Principal Investigators and coordinated at the University of California, San Francisco. HERS is the largest trial of any intervention to reduce the risk of recurrent CHD events in women with heart disease and is the first controlled trial to seek evidence of the efficacy and safety of postmenopausal hormone therapy to prevent recurrent CHD events. *Controlled Clin Trials* 1998;19:314–335 © Elsevier Science Inc. 1998

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INTRODUCTION

Coronary heart disease (CHD) is the most common cause of mortality in women over 50 years of age in the United States [1]. A 50-year-old woman today has about a 46% lifetime probability of developing CHD and a 31% chance of dying from it [2]. Many observational studies have found that oral postmenopausal estrogen therapy is associated with a 35–50% reduction in risk of CHD [2–4]. The apparent protective effect of estrogen therapy may be even stronger in women who already have CHD [5].

The reported association between postmenopausal estrogen therapy and reduced CHD risk, though consistent, biologically plausible, and strong, could be confounded if women taking estrogen have a more favorable cardiovascular risk profile than nonusers [6, 7]. Only a comparison of hormone use and placebo in women who are randomly assigned to therapy can provide definitive evidence that treatment reduces the risk of CHD. We are therefore conducting the Heart and Estrogen/progestin Replacement Study (HERS), a randomized, double-blind trial of the effect of estrogen plus progestin therapy on the frequency of sudden cardiac death and myocardial infarction among postmenopausal women with known CHD.

METHODS

Participants

Participants in the HERS are 2763 postmenopausal women ⩽79 years old who have a uterus and who have CHD evidenced by prior myocardial infarction, coronary artery bypass graft surgery, mechanical revascularization, or angiographic evidence of at least a 50% occlusion of one or more major coronary arteries.

Women were excluded if their reported CHD event had occurred within 6 months of randomization, if they had used postmenopausal hormone therapy within 3 months of the initial screening, if hormone therapy was thought to be contraindicated, if they were participating in another trial, or if they were thought to be unlikely to adhere to the protocol (Table 1).

Women of any race were included. Aspirin or other anticoagulant, antihypertensive, antianginal, and lipid-lowering drugs are allowed. Use of these drugs during follow-up is assessed carefully, but no effort is made to modify these treatments. Women with elevated diastolic (⩾90 mm Hg) or systolic (⩾140 mm Hg) blood pressures, low-density lipoprotein cholesterol ⩾130 mg/dL, fasting blood sugar ⩾140 mg/dL, and women who smoked cigarettes were told their risk factor levels and referred to their private physicians for evaluation

Table 1 The Heart and Estrogen/progestin Replacement Study Inclusion and Exclusion Criteria

Inclusion Criteria

- ⩽79 years old
- Uterus present
- Postmenopausal based on one or more of the following:
  1. ⩾55 years and no natural menses for at least 5 years
  2. no natural menses for at least 1 year and serum FSH > 40 mIU/ml
  3. documented bilateral oophorectomy
  4. reported bilateral oophorectomy, FSH > 40 mIU/ml and estradiol < 25 pg/ml
- Evidence of coronary disease based on one or more of the following as documented by baseline ECG or hospital discharge summary:
  1. definite myocardial infarction 6 or more months before randomization
  2. coronary artery bypass surgery 6 or more months before randomization
  3. mechanical coronary revascularization 6 or more months before randomization
  4. angiographic evidence of 50% or greater luminal diameter narrowing of any one or more major coronary artery segments

Exclusion Criteria

- Myocardial infarction, coronary artery bypass surgery, or mechanical revascularization within 6 months of randomization
- Used oral, parenteral, vaginal, or transdermal hormones within 3 months of the preliminary screening visit
- Serum triglycerides ⩾ 300 mg/dL
- History of deep-vein thrombosis or pulmonary embolism
- History of breast cancer or clinical breast examination or mammogram suggestive of breast cancer*
- History of endometrial cancer
- Abnormal uterine bleeding, any endometrial hyperplasia or endometrium > 5 mm in thickness on transvaginal ultrasound
- Papanicolaou smear abnormal (SIL I, II, or III, carcinoma in situ, or cancer), or unobtainable
- SGOT more than 1.2 times normal
- Unlikely to remain geographically accessible for study visits for at least 4 years
- Disease (other than coronary disease) judged likely to be fatal within 4 years
- New York Heart Association class IV or severe class III congestive heart failure
- Alcoholism or drug abuse
- Uncontrolled hypertension (diastolic blood pressure ⩾ 105 mm Hg or systolic blood pressure ⩾ 200 mm Hg)
- Uncontrolled diabetes (fasting blood sugar ⩾ 300 mg/dL)
- Participation in any other investigational drug or device study
- Compliance with placebo medication during run-in phase < 80%
- History of intolerance to hormone replacement therapy
- Any preexisting condition that, in the opinion of the investigator, indicates that the participant would not be an appropriate candidate for long-term hormone replacement or placebo therapy

*Breast examination revealing a suspicious mass, skin change, or nipple discharge is considered suspicious of breast cancer. Mammograms are classified as normal (no evaluation required other than routine screening); abnormal requiring short-interval mammogram (shorter than the routine 12-month screening interval); and abnormal requiring immediate evaluation. At baseline, any abnormal mammogram was considered suggestive of cancer.

and treatment. Those with a history of postmenopausal fracture were informed during the consent process of evidence suggesting that estrogen therapy may prevent further fractures and progression of osteoporosis.

Recruitment

We planned an 18-month recruitment phase, which began in January 1993. Various recruitment methods were employed, including enriched lists of cardiac patients, mass mailings, and direct advertising. Because recruitment for HERS was more difficult than expected, halfway through the recruitment phase, we extended the recruitment period by 3 months and added three additional clinical centers. By September 30, 1994, HERS had enrolled 2763 women, 423 more than our goal of 2340.

Baseline Visits

A screening telephone call and three baseline clinic visits were required to assess eligibility and collect baseline data. At the first visit, informed consent was obtained, eligibility was determined, and data were collected on demographic characteristics, reproductive and health history, and risk factors for CHD, breast cancer, and osteoporosis. Total serum cholesterol, triglyceride, fasting glucose and glutamic oxaloacetic transaminase (SGOT) levels were measured by SmithKline Beecham Clinical Laboratories. Lipoprotein values measured by SmithKline Beecham Clinical Laboratories were used only to determine eligibility. Serum samples for baseline lipoprotein measurements were prepared at the clinical sites and shipped frozen to the Lipoprotein Analytical Laboratory at Johns Hopkins Hospital where reference methods were used to determine total cholesterol, triglyceride, high-density lipoprotein cholesterol, and lipoprotein(a) levels. Serum was frozen and stored at the Lipoprotein Analytical Laboratory for future measurements. Follicle-stimulating hormone and estradiol levels were measured if it was necessary to confirm postmenopausal status.

At the second visit, eligibility was further evaluated and data were collected on quality of life (symptoms potentially related to hormone therapy, mood, functional ability, activities of daily living, sexual function, and urinary function) and medication use. Potential participants underwent gynecologic examination including breast and pelvic examination, Papanicolaou smear, and endometrial evaluation (endometrial aspiration biopsy, if possible; if not, transvaginal ultrasound). A screening mammogram was scheduled or performed at this visit and a 4- to 8-week placebo run-in period began. At the second or third screening visit, women had a general physical examination that included measurement of height, weight, blood pressure, pulse, and waist and hip circumferences and a cardiac examination that included evaluation of the lungs, jugular venous pressure, heart and extremities. A standardized 12-lead ECG was performed. Finally, eligibility was reviewed, including the results of the endometrial evaluation and mammogram.

Randomization

At the end of the third baseline clinic visit, eligible participants were assigned with equal probability to one of the two treatment groups. Randomization was stratified by clinical center, and within-strata treatment was randomized in blocks of fixed size.

Intervention

Participants take one tablet containing both conjugated estrogens (Premarin 0.625 mg) and medroxyprogesterone acetate (Cycrin 2.5 mg) or one identical placebo tablet daily. A continuous combined regimen was chosen for convenience and to avoid cyclic bleeding that could lead to unblinding. Most observational data from the United States suggesting that estrogen prevents CHD are derived from women who took oral conjugated estrogen, and most hormone-treated women in the United States (about 70%) use this agent. Medroxyprogesterone acetate, which has been proven to prevent endometrial hyperplasia while having relatively little adverse effect on lipoprotein profiles, [8, 9] is the most commonly used progestin in the United States.

Blinding

Participants, as well as staff at the clinical centers, Wyeth-Ayerst, and the study laboratories, are blinded to treatment assignment, as are the members of the independent Morbidity and Mortality Committee. The individual treatment codes are known only by three persons at the coordinating center who prepare unblinded analyses for the Data and Safety Monitoring Board and have no contact with the clinical centers or participants. During the trial, unblinded results by treatment group are known only by members of the Data and Safety Monitoring Board, key coordinating center personnel, and the chair of the Steering Committee.

To prevent unblinding of clinical center staff, breast problems and endometrial bleeding are evaluated in a separate gynecology clinic. All breast and vaginal bleeding problems are reported directly to a gynecology staff member who does not communicate with clinical center personnel about breast or gynecologic problems, but who interacts directly with participants and the coordinating center. The gynecology staff do not participate in ascertainment of cardiovascular outcomes. Because endometrial biopsy may be indicated in placebo-treated women who have vaginal bleeding but not in hormone-treated women, the gynecologists are allowed to be unblinded to treatment status in certain rare situations with prior approval of a designated coordinating center physician who remains blinded to the woman's treatment assignment.

Follow-up Visits

During the intervention phase of the trial, follow-up visits to the clinical center are scheduled every 4 months to assess and encourage compliance with study drug treatment, assess side effects, and obtain outcome information. Annual evaluations at the clinical center repeat the health, risk factor, and

quality of life questionnaires, general and cardiac examinations, and standard ECG. Fasting glucose, lipids, and SGOT are measured at the first and final annual visits, and serum samples are obtained at these times and at the third annual visit for storage (Table 2).

An ECG is performed at any HERS clinic visit at which a participant reports either an interval cardiac hospitalization or an episode of chest pain suggestive of myocardial ischemia. ECGs obtained at the clinical sites are acquired using highly standardized lead placement techniques and a Mac PC electrocardiograph machine (Marquette Electronics, Milwaukee, WI). These ECGs are transmitted electronically to EPICARE, the central ECG reading facility, where they are analyzed using computer programs. All ECGs obtained electronically are compared with the ECGs obtained at randomization for changes that suggest new, possibly silent, myocardial infarction. ECG evidence of possible myocardial infarction includes grade 2 or higher Q-wave changes, grade 1 Q-wave changes associated with significant evolution of ST-T changes, profound evolution of ST-T changes without Q-waves, or new left-bundle branch block with QRS duration increase exceeding 20 msec [10].

Separate annual follow-up visits to the study gynecologist include repeat breast examinations, pelvic examinations with Pap smears, and screening mammograms. The second and final annual visits include repeat endometrial evaluations.

Outcomes

CHD events (fatal or nonfatal myocardial infarction, sudden CHD death, or other CHD death) are the primary outcome of the trial. In participants with anginal pain or anginal-equivalent syndromes, the diagnosis of myocardial infarction is made in the presence of marked ischemic ECG changes ($\geqslant$grade 2 Q-wave change or grade 1 Q-wave change with evolutionary ST-T changes); cardiac enzyme elevation (rise in total creatine kinase over twice the upper limit of normal with positive myocardial bands); or borderline cardiac enzyme elevation (typical temporal change in creatine kinase without otherwise meeting the criteria for elevation) and probable ischemic ECG changes (evolutionary ST-T changes or new left-bundle branch block with QRS duration increase exceeding 20 msec). In participants with no ischemic symptoms, diagnosis of acute myocardial infarction is made in the presence of Q-wave change of grade 2 or higher (silent myocardial infarction); a grade 1 Q-wave change and borderline cardiac enzyme elevation; or probable ischemic ECG changes and cardiac enzyme elevation. Myocardial infarction is also diagnosed if there is evidence of fresh myocardial infarction at autopsy.

Death is considered due to myocardial infarction if a participant dies following the onset of chest pain typical of acute myocardial ischemia associated with ST segment elevation on the ECG or during the same hospitalization in which a documented acute myocardial infarction has occurred. Sudden CHD death is defined as an unexpected, nontraumatic, non–self-inflicted death that occurs within 1 hour of the onset of the terminal symptoms. Other CHD deaths are those judged by the Morbidity and Mortality Committee to be due to CHD but that cannot be definitely classified as acute myocardial infarction or sudden death.

Table 2 Data Collection Components of HERS Visits

Procedure	Baseline	Every 4 mos.	1st AV[a]	2nd AV	3rd AV	4th AV	Last AV
Telephone screenings form	X						
Informed consent	X						
Health questionnaire	X		X	X	X	X	X
Blood lipoproteins/stored serum	X		X		X		X
Chemistry panel	X		X				X
FSH/estradiol (if needed)	(X)						
Quality of life	X	X (1st only)	X	X	X	X	X
Medication use	X	X	X	X	X	X	X
Pelvic exam/Papanicolaou smear	X		X	X	X	X	X
Endometrial evaluation	X			X			X
Mammogram	X		X	X	X	X	X
Run-in	X						
Bleeding diary	X	X	X	X	X	X	X
Physical examination	X		X	X	X	X	X
Electrocardiogram	X		X	X	X	X	X
Pill count	X	X	X	X	X	X	X
Outcome and side effect evaluation		X	X	X	X	X	X

[a] AV = annual visit.

Table 3 The Heart and Estrogen/progestin Replacement Study: Outcome Events

Primary Outcome
- definite coronary heart disease death
  -death due to acute myocardial infarction
  -sudden coronary death
  -other coronary disease death
- nonfatal myocardial infarction (symptomatic and silent)

Secondary Outcomes

Coronary Disease
- coronary artery bypass surgery
- mechanical coronary revascularization
- hospitalization for unstable angina
- hospitalization for congestive heart failure
- resuscitated cardiac arrest

Vascular Disease
- stroke and transient ischemic attack
- peripheral arterial disease

Cancer
- endometrial hyperplasia and cancer
- breast cancer
- ovarian cancer

Thromboembolism
- pulmonary embolism
- deep-vein thrombosis

Gallbladder disease

Fractures

Deaths
- cancer deaths
- noncoronary disease, noncancer deaths
- total deaths

Uterine Bleeding

Side Effects
- vasomotor symptoms
- genitourinary symptoms
- bloating
- breast tenderness
- headache
- weight gain

In addition to these primary outcomes, the occurrence of various secondary outcome events is recorded (Table 3). Participants are classified, according to reports of procedures, as having coronary bypass surgery or mechanical coronary revascularization. Hospitalization for unstable angina is diagnosed in participants who are admitted to the hospital for management of anginal chest pain or an anginal equivalent but found not to have a myocardial infarction. Participants are classified as hospitalized for congestive heart failure when the admitting diagnosis is congestive heart failure, pulmonary edema, or low cardiac output. Resuscitated cardiac arrest occurs when resuscitation is successful in cases without evidence of acute myocardial infarction that would otherwise qualify as sudden death. Stroke is defined as the rapid onset of a persistent neurologic deficit attributed to obstruction or hemorrhage that is not due to brain trauma, tumor, infection, or other cause. The deficit must last more than

24 hours unless death intervenes or there is a demonstrable lesion compatible with an acute stroke on head CT or MRI scan. Transient ischemic attack is a similar neurologic deficit that resolves within 24 hours. Peripheral arterial disease is defined as acute arterial obstruction, dissection or rupture (except for the coronary arteries), noncardiac arterial vascular surgery, or amputation for arterial vascular insufficiency. Breast, ovarian, and other cancers are diagnosed on the basis of local pathology reports without central review. Diagnoses of endometrial hyperplasia and cancer are based on central review of pathology slides. Pulmonary embolism must be documented either by lung scanning indicative of a high probability of pulmonary embolism or by pulmonary angiography; deep-vein thrombosis includes thrombosis of the popliteal or more proximal veins of the legs as documented by venography, impedance plethysmography, or ultrasound. Participants who undergo cholecystectomy or bile duct exploration documented by operative procedure or who have symptomatic gallstone disease documented by appropriate imaging studies are classified as having gallbladder disease. Diagnosis of fracture requires a radiology report noting a definite fracture. Uterine bleeding is recorded in a daily diary as none, spotting (defined as requiring no sanitary protection or a panty liner only), or bleeding (defined as heavy enough to require a sanitary napkin). Side effects are assessed by a questionnaire administered at the first 4-month follow-up visit and annually thereafter.

The clinics notify the Coordinating Center of any hospitalization, death, or suspected primary or secondary event. They then complete a brief event form, thus triggering a series of data collection efforts that include contacting the woman's physician and acquiring copies of the hospital's ECGs and discharge summaries. Information on out-of-hospital deaths includes standard interviews with the woman's physician, family members, and witnesses.

Data from all deaths and all suspected primary outcome events, including abnormal ECG findings detected on computerized evaluation of routine annual ECGs, are reviewed under blinded conditions and classified according to written guidelines based on the criteria outlined above by an independent Morbidity and Mortality Committee whose members have relevant expertise in cardiology, epidemiology, and medicine. All possible events (including possible silent myocardial infarction) are reviewed independently by two members of the committee. Cases in which the two reviewers disagree are settled by discussion, if necessary, involving the full Morbidity and Mortality Committee.

All suspected secondary events are reviewed independently by two blinded physicians at the Coordinating Center. Cases in which the two reviewers disagree are settled by discussion, if necessary including a third, blinded Coordinating Center physician.

Adverse Events

Participants are questioned about possible adverse events at each 4-month follow-up visit and asked to notify the clinical center of any adverse effect, illness, medical procedure, or hospitalization and to notify the HERS gynecologist of breast complaints or uterine bleeding. For any adverse experience reported during the study, the nature, duration, intensity, and any remedial action taken are recorded. Serious adverse effects are reported to Wyeth-Ayerst

and the Coordinating Center within 24 hours after clinical center staff learn of the event. The Data and Safety Monitoring Board reviews information on all adverse experiences.

Uterine Bleeding and Endometrial Abnormalities

All women are requested to note uterine bleeding on a daily calendar and call the gynecologist if they have bleeding or breast problems. Because all women had a normal baseline endometrial evaluation (aspiration biopsy or, if not possible, transvaginal ultrasound), endometrial evaluation is not repeated for uterine spotting during the first 6 months of therapy but may be done at the discretion of the gynecologist for heavy bleeding.

Any uterine bleeding is abnormal in women taking placebo, so these women generally require endometrial evaluation if bleeding occurs more than 6 months after the baseline endometrial evaluation. In contrast, spotting during the first year of therapy is not uncommon in women taking combined continuous hormone therapy and rarely reflects endometrial hyperplasia or cancer [8, 9, 11]. Thus, a study gynecologist who feels that knowledge of the participant's treatment status would determine whether or not endometrial evaluation should be performed may request permission from the Coordinating Center to unblind. After reviewing the case, the Coordinating Center physician authorizes unblinding if knowledge of treatment status would determine whether the participant requires an invasive procedure. As at baseline, endometrial evaluation begins with an attempted endometrial biopsy. For women in whom endometrial biopsy cannot be completed, transvaginal ultrasound is performed. If the endometrium is abnormally thick (>5 mm for both layers of the endometrium at the thickest anteroposterior diameter, the longitudinal dimension), dilation and fractional curettage is performed to obtain endometrial tissue.

Endometrial biopsy tissue is reviewed locally at each clinical center. If the tissue is classified as endometrial hyperplasia or cancer, the slides are reviewed centrally. Final classification of endometrial hyperplasia and cancer is based only on the central evaluation.

Discontinuation or Suspension of Study Treatment

The study treatment is discontinued but follow-up continued for women who develop any of the following conditions: simple endometrial hyperplasia without atypia that does not respond to treatment with medroxyprogesterone acetate; hyperplasia with atypia; endometrial, cervical, breast, or ovarian cancer; deep-vein thrombosis; pulmonary embolism; or cholecystitis. Women with cholecystitis who undergo cholecystectomy are allowed to resume the study treatment. Women who experience any severe illness may have study medications discontinued temporarily and may resume treatment when the investigator and primary care physician agree that it is appropriate.

Data Analysis

The primary null hypothesis is that the incidence of CHD events in women randomly assigned to receive estrogen plus progestin therapy does not differ

Table 4 Heart and Estrogen/progestin Replacement Study Assumptions for Sample Size Estimation

1. Coronary disease event rate in the placebo group = 5% per year
2. Half of the protective effect of hormone therapy is due to changes in lipids that alter coronary disease rates only after a lag time of 2 years
3. Power = 90%, two-tailed type I error = 0.05
4. Average follow-up of 4.75 years
5. Loss to follow-up and noncoronary disease death = 2% per year
6. Crossover as follows:

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Active to placebo	5%	4%	3%	2%	2%	2%
Placebo to active	1%	1%	1%	1%	1%	1%

from the incidence in women randomly assigned to receive placebo. The primary analysis compares the rate of CHD events among women assigned to active medication with the rate among women assigned to placebo using a log-rank test for time to first CHD event; treatment assignment is the only predictor. The analysis will be by intention to treat, categorizing participants according to treatment assignment, regardless of compliance. The validity of the randomization will be assessed by comparing treatment and placebo groups on the full range of baseline variables. Participants lost to follow-up will be censored at the last date at which they are known to be alive without a recurrent CHD event, and sensitivity analyses will be carried out to assess the potential effects of informative censoring. The proportional hazards assumption will be verified by testing for interaction between the treatment effect and follow-up time.

Possible baseline predictors of study outcomes will be examined using Cox models controlling for treatment assignment as well as baseline covariates. Potential mediators of the treatment effect will be assessed by comparing the estimated relative hazard for treatment in a Cox model adjusted for the proposed mediator (measured after randomization) to the corresponding estimate from an unadjusted model. Attenuation of the estimated relative hazard for treatment would be consistent with a mediating effect. Secondary analyses of more broadly defined CHD endpoints, all-cause mortality, and outcomes possibly related to HRT (such as breast cancer, gallbladder disease, deep-vein thrombosis, and pulmonary embolism) will also be carried out using unadjusted Cox models. Treatment effects on common recurrent events, in particular unstable angina, will be analyzed using the Anderson-Gill extension of the Cox model [12].

Sample Size Estimates

Although we will use proportional hazards models for the primary analysis, we approximated sample size using standard formulae for two-group comparisons of proportions, with assumptions noted in Table 4. The expectation of a 5% per year CHD event rate in the placebo group was based on data from several observational studies and intervention trials in women with CHD [5, 13–18]. To ensure conservative estimates, we relied primarily on CHD event

rates among women in recent randomized trials, as these rates tend to be lower than recurrence rates in the general population.

How estrogen might prevent coronary events is not clear, but at least part of the effect may be through an improved lipoprotein profile [8]. We estimated that half of the protective effect of hormone therapy is due to changes in lipid levels [19, 20] that alter CHD rates only after a lag time of 2 years. Loss of follow-up and deaths due to non-CHD causes were assumed to occur in 2% of participants per year. The proportion with events in the hormone-treated groups was adjusted to reflect the expected number of person-years on each of the treatments after incorporating the crossover and lag-time assumptions listed in Table 4.

Observational data suggest that treatment with unopposed estrogen is associated with a 35–50% reduction in the rate of CHD events in healthy women [3, 4] and possibly a larger reduction in women with CHD [5]. The full benefit may not be realized in the intervention setting, and the addition of a progestin to the estrogen regimen might decrease the beneficial effect of estrogen on serum lipid levels; therefore, we elected to estimate a 35% reduction in coronary events in hormone-treated women compared with placebo-treated women. This estimated true effect size translates to an observed effect size of 24% when the impacts of crossover and loss to follow-up are incorporated.

We estimated that if the last woman randomized were followed for approximately 4 years, the mean follow-up time for the cohort would be 4.75 years. Given these assumptions, we needed to enroll a total (for both groups) of 2340 women to have a power of 90% at a two-tailed Type I error rate.

We actually recruited 2763 participants, 18% more than our sample size estimate; however, because we extended the recruitment period by 3 months and enrolled most of participants in the last half of the recruitment period, we now estimate that the 2763 HERS participants will be followed for an average of 4.2 years. The 18% increase in sample size counters the 12% decrease in projected person-years of follow-up, which is now estimated to be 11,711 person-years.

Interim Monitoring

The members of the HERS Data and Safety Monitoring Board have expertise in clinical trials, statistics, epidemiology, gynecology, ethics, cardiology, and internal medicine. The board monitors recruitment, compliance, randomization, outcomes, and adverse experiences. Analyses are performed using an alpha-spending function [21] to set interim stopping boundaries in a way that maintains an overall type I error rate close to 0.05 after interim monitoring. The particular function that we chose yields stopping boundaries consistent with those proposed by O'Brien and Fleming [22]. The proportion of data collected at each interim analysis time is the observed participant-years of observation at interim analysis divided by the expected total participant-years.

The Coordinating Center performs all analyses for the Data and Safety Monitoring Board. Only three individuals at the Coordinating Center know the individual treatment codes. The Data and Safety Monitoring Board, a few key Coordinating Center personnel, and the chairperson of the Steering Committee are the only people who see unblinded results. The Data and Safety

Monitoring Board, which is responsible for recommendations to alter the study protocol or terminate the trial early, must approve any alteration of the trial protocol proposed by the investigators.

Study Organization, Clinical Centers, and Core Laboratories

The Coordinating Center at the University of California, San Francisco, is responsible for the quality of all aspects of the design and implementation of the study and of the analysis and dissemination of findings. The 20 clinical center investigators are responsible for recruiting, evaluating, treating, and following the study subjects, for collecting high-quality data, and for participating in the scientific aspects of the study, including design, analysis, and publication.

The Steering Committee, composed of the principal investigators of the clinical centers, the ECG laboratory, the lipid laboratory, and representatives of Wyeth-Ayerst Laboratories and the Coordinating Center, provides scientific direction for the trial. An Executive Committee meets regularly by telephone to make decisions between Steering Committee meetings. Representatives from the collaborating investigators and clinical staff, the Coordinating Center, and Wyeth-Ayerst serve on six subcommittees: Recruitment and Retention; Quality Control, Data, and Laboratories; Clinical Quality Control; Design, Analysis, and Publications; Gynecologic Management; and Cardiovascular Disease Management and Endpoints.

All data regarding primary and secondary outcomes are collected by the Coordinating Center directly from the clinical sites. Other data recorded on case report forms are reviewed, collected, entered, and edited by Wyeth-Ayerst Laboratories. The dataset is transferred periodically from Wyeth-Ayerst to the Coordinating Center, which prepares reports for the Data and Safety Monitoring Board and analyses for scientific presentation and publication.

Core laboratories include SmithKline Beecham Clinical Laboratories; the Lipoprotein Analytical Laboratory at Johns Hopkins University in Baltimore, MD (Paul Bachorik, PhD, Director); and EPICARE, the ECG reading center at Wake Forest University School of Medicine in Winston-Salem, NC (Penti Rautaharju, MD, Director); Dr. Robert Kurman, MD, at Johns Hopkins University reviews all abnormal endometrial pathology (see Figure 1).

RESULTS

HERS investigators contacted 68,561 women by telephone and briefly interviewed them concerning potential eligibility and willingness to participate. Of those interviewed, 21% were ineligible because they had had a hysterectomy, 21% reported that they did not have CHD, and 51% were ineligible for other reasons or were not willing to participate. Of 4830 women who attended the first screening visit, 6% were excluded because they did not have documented heart disease, 5% were excluded because their serum triglyceride, SGOT, or fasting glucose did not meet the study eligibility criteria, and 18% were excluded for a variety of other reasons or did not return for the second visit. At the second screening visit, 3463 women were evaluated; 5% were excluded because

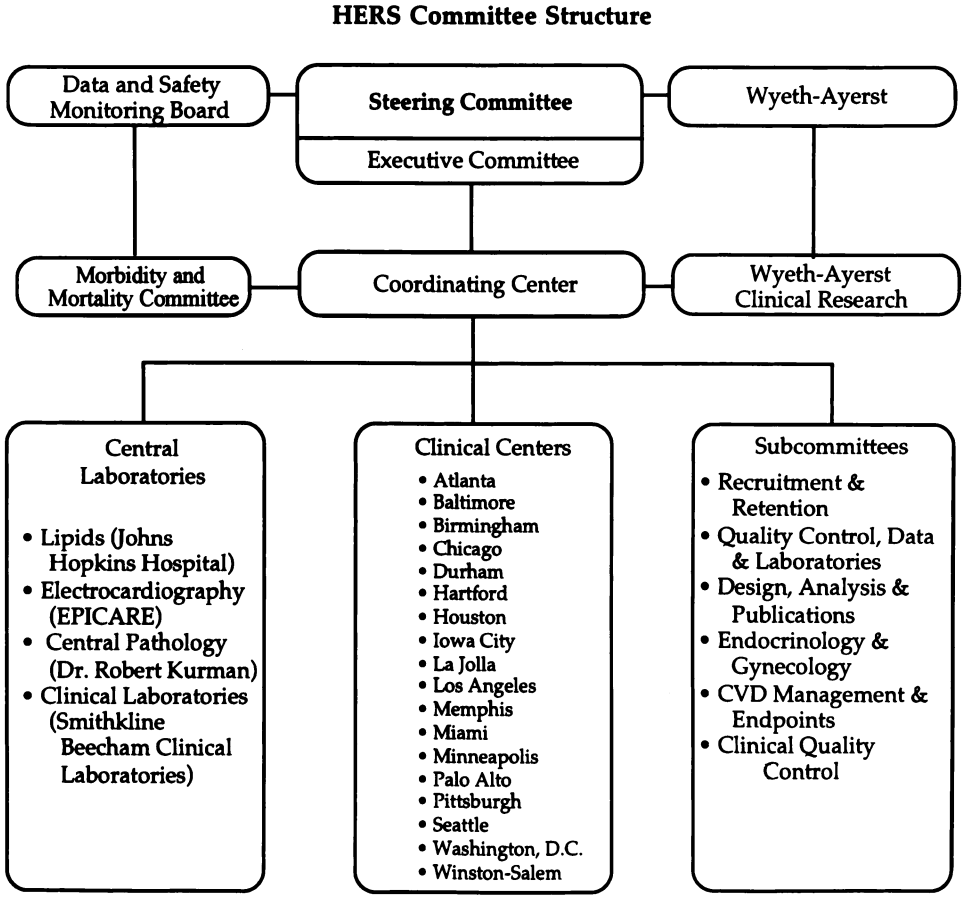

Figure 1 HERS organizational structure.

of abnormal breast or gynecologic findings, 3% because of abnormal mammograms, and another 12% for a variety of other reasons or because they refused to continue. Thus, 2780 women were still eligible at the end of the second screening visit, and they entered the placebo run-in phase of the trial.

Fourteen women did not return for the final screening visit when randomization was performed. The only additional reason for exclusion at this visit was lack of compliance with placebo run-in therapy. Only three women were excluded at this visit because their tablet count revealed that they had taken less than 80% of the placebo medication. Thus, 2763 eligible women were randomized, 57% of the prospective participants evaluated at the first screening visit. The number of participants enrolled varied among the clinical centers, ranging from 56 to 290.

Most women enrolled in the HERS have CHD documented by the narrowing of one or more coronary arteries on angiography (Table 5). About 39% of the women also have had documented myocardial infarction, 37% have had coronary bypass graft surgery, and 39% have had transluminal coronary revascularization. Participants range in age from 44 to 79 years, with a mean age of

Table 5 Entrance Criteria for 2763 Participants in the Heart and Estrogen/progestin Replacement Study

Entrance Criteria	Number	Percent[a]
Myocardial infarction 6 or more months before randomization	1068	39
50% or greater narrowing of one or more major coronary artery	2269	82
Documented history of coronary artery bypass graft surgery	1018	37
Documented history of transluminal mechanical revascularization	1081	39

[a] Percents total more than 100 because some participants met more than one entrance criterion and categories are not mutually exclusive. In addition, clinic staff were required to document that women met at least one inclusion criterion but were not required to document the presence or absence of each criterion.

66.7 (SD 6.7) years. Most participants were white (89%), married (57%), and had completed high school or some college (80%) (Table 6). The mean age at menopause was 48.7 (SD 5.0 years). Despite the fact that all participants had documented CHD, 76% reported excellent, very good, or good health.

Most of the women (62%) were past or current smokers, with 13% reporting that they currently smoked cigarettes regularly (Table 7). The mean number of pack-years was 30 among the past smokers and 39 among the current smokers. Almost 60% of the women reported hypertension. Systolic blood pressure was 140 mm Hg or above in 38% of the women and above 160 mm Hg in about 10%. Diastolic blood pressure was 90 mm Hg or above in only 5% of the women, and only three women had diastolic pressure above 100 mm Hg. Despite having CHD, 48% of the women had HDL cholesterol of 50 mg/dL or above, and only 21% had HDL cholesterol levels below 40 mg/dL. LDL cholesterol levels were 100 mg/dL or above in 90% of participants and 160 mg/dL or above in 31%. Diabetes was reported by 23% of subjects, with 10% using insulin. Two thirds (64%) reported that they attended an exercise program or walked for exercise regularly, and 39% exercised more than three times per week. About 34% of the cohort was obese or severely obese. Waist/hip ratio was above 0.9 in 34% and above 1.0 in 5%. About 40% of the cohort consumed at least one or two drinks per day.

DISCUSSION

Coronary disease is the leading cause of death in postmenopausal women. Extensive observational evidence indicates that estrogen therapy reduces risk for CHD, but these findings might be due to confounding factors if women who choose to take estrogen are healthier than those who do not. Only a randomized trial can answer this question, and we believe that evidence from a randomized trial is necessary before recommending postmenopausal hormone therapy to prevent CHD.

The HERS is a secondary prevention trial in postmenopausal women with documented CHD. A secondary prevention trial is more feasible and cost-effective than a primary prevention trial in healthy women because women with CHD have a much higher incidence of CHD events than healthy women, allowing a much smaller sample size. Also, hormone therapy may be more effective in women with CHD than in healthy women [5]. The results of the HERS will provide important information on the effectiveness of hormone

Table 6 Characteristics of 2763 Participants in the Heart and Estrogen/progestin Replacement Study[a]

Characteristic	Number	Percent
Age (years)		
<50	18	1
50–59	421	15
60–69	1305	47
70–79	1019	37
Ethnicity		
White	2451	89
African-American	218	8
Hispanic	54	2
Asian	21	<1
Other	19	<1
Marital status		
Married	1588	57
Divorced/separated	381	14
Widowed	714	26
Never married	80	3
Education (years)		
0–11	565	21
12	1091	39
13–15	668	24
16	213	8
>16	224	8
Number of pregnancies		
0	198	7
1–2	682	25
3–4	1022	37
⩾5	861	31
Age at menopause (years)		
⩽45	659	24
45–49	629	23
50–54	1175	43
⩾55	299	11
General health		
Excellent	113	4
Very good	674	24
Good	1307	47
Fair	605	22
Poor	60	2

[a] Data based on HERS database as of November 12, 1996. Final edited data may differ slightly. Percentages may not add up to 100 because of rounding.

therapy in preventing recurrent events in women with CHD. The findings from HERS may not be fully generalizable to women without heart disease, but we believe they will contribute to more general inferences about the coronary efficacy of hormone replacement therapy.

Among women with a uterus who take unopposed estrogen, the risk of developing endometrial hyperplasia [8] and endometrial cancer is increased markedly [23]. Adding a progestin to the estrogen regimen prevents the development of endometrial hyperplasia [8, 9, 11] and cancer [23]. In clinical practice, the choice of hormone regimen is usually determined by whether a woman

Table 7 Prevalence of Cardiac Risk Factors Among 2763 Participants in the Heart and Estrogen/progestin Replacement Study[a]

Risk Factor	Number	Percent
Cigarette smoking		
Never smoked	1051	38
Past smoker	1352	49
Current smoker	360	13
History of hypertension	1619	59
Systolic blood pressure (mm Hg)		
<140	1712	62
140–160	783	28
>160	267	10
Diastolic blood pressure (mm Hg)		
<90	2613	95
90–100	146	5
>100	3	<1
Total cholesterol (mg/dL)		
<200	660	24
200–<240	1110	40
240–<300	856	31
⩾300	133	5
HDL cholesterol (mg/dL)		
<40	567	21
40–<50	871	32
50–<60	763	28
⩾60	551	20
LDL cholesterol (mg/dL)		
<100	262	9
100–<130	745	27
130–<160	901	33
⩾ 160	844	31
Triglycerides (mg/dL)		
<150	1269	46
150–199	691	25
200–249	443	16
250–299	356	13
Diabetes		
Insulin use	273	10
No insulin use	361	13
Exercise regularly		
1–3 times per week	702	25
>3 times per week	1068	39
Body mass index		
<27.5 (normal)	1330	48
27.5–30 (moderately obese)	486	18
30–40 (obese)	842	31
>40 (severely obese)	100	4
Waist/hip ratio		
<0.8	549	20
0.8–0.9	1273	46
>0.9–1.0	786	29
>1.0	152	5
Alcohol consumption (drinks per day)		
0 (no alcohol in past 30 days)	1668	60
1–2	1004	36
3–4	84	3
⩾5	7	<1

[a] Data based on HERS database as of November 11, 1996. Final edited data may differ slightly. Percentages may not add up to 100 because of rounding.

has a uterus; women who have had a hysterectomy are treated with estrogen alone, and those with a uterus are treated with estrogen plus progestin. Because all women enrolled in HERS have a uterus, we added medroxyprogesterone acetate to the estrogen regimen.

If combination therapy is effective in reducing CHD risk, we will assume that the benefit is due to the estrogen, not to the progestin component. Unopposed estrogen might possibly be more effective than combination therapy for prevention of CHD. If so, our findings may underestimate any protective effect of unopposed estrogen therapy; however, given the increased risk of endometrial hyperplasia and cancer associated with unopposed estrogen use, it is unlikely that this regimen would be widely adopted by women with a uterus. Our study design does not allow comparison of estrogen alone to estrogen plus medroxyprogesterone acetate. If estrogen plus progestin therapy is not effective in reducing the risk of CHD events in the HERS, we will not be able to determine whether this lack of effect occurs because estrogen does not reduce the risk of CHD events or because adding progestin to the estrogen regimen negates the benefit of estrogen.

Most of the women enrolled in the trial are taking multiple medications for treatment of CHD or for established risk factors associated with CHD. If some of these medications, such as lipid-lowering medications or aspirin, have the same mechanism of action as estrogen, the effect of therapy may be diminished. Because only 10% of the women enrolled in the HERS are nonwhite, the generalizability of the study findings will be limited if estrogen therapy has different effects in nonwhite women.

The Postmenopausal Estrogen Progestin Interventions Trial (PEPI) was a randomized trial in 875 postmenopausal women to determine the effects of 3 years of treatment with estrogen and various estrogen plus progestin regimens on CHD risk factors such as serum lipoprotein levels, blood pressure, fasting glucose, insulin, and fibrinogen [8]. The PEPI participants were younger than the women enrolled in HERS (less than 65 years old at enrollment) and did not have heart disease. The most important difference between HERS and PEPI is that PEPI was not designed to evaluate the effect of HRT on CHD events. The Women's Health Initiative (WHI) Randomized Trial [24] is a primary prevention trial to determine whether hormone therapy reduces the risk of CHD events in healthy women. The WHI will enroll approximately 25,000 women. Those without a uterus will be randomized to conjugated equine estrogen 0.625 mg daily or placebo. Women with a uterus will be randomized to estrogen plus medroxyprogesterone acetate 2.5 mg daily or placebo. The intervention in the WHI is planned to continue for 9 years, so its results are not expected before the year 2005.

The HERS is the largest trial of any intervention to reduce the risk of recurrent CHD events in women with heart disease and the first to seek controlled clinical trial evidence of the efficacy and safety of postmenopausal hormone therapy to prevent recurrent CHD.

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REFERENCES

1. Thom TJ. Cardiovascular disease mortality among United States women. In: Eaker ED, Packard B, Wenger NK, et al., eds. *Coronary Heart Disease in Women.* Proceedings of an NIH workshop. New York: Haymarket Doyma; 1987:33–41.
2. Grady D, Rubin S, Petitti D, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–1037.
3. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47–63.
4. 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*. Sereno Symposia; Norwell, Massachusetts; 1990:211–223.
5. Sullivan J. Estrogen replacement and coronary artery disease. *Arch Intern Med* 1990;150:2557–2562.
6. Cauley J, Cummings SR, Black DM, et al. Prevalence and determinants of estrogen replacement therapy in elderly women. *Am J Obstet Gynecol* 1990;163:1438–1444.
7. Barrett-Connor E. Postmenopausal estrogen and prevention bias. *Ann Intern Med* 1991;115:455–456.
8. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA* 1995;273:199–208.
9. Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. *JAMA* 1996;275:370–375.
10. Rautaharju P, Calhoun H, Chaitman B. Novacode serial ECG classification system for clinical trials and epidemiological studies. *J Electrocardiol* 1992;34(suppl):179–187.
11. Archer D, Pickar J, Bottiglioni F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. *Obstet Gynecol* 1994;83:686–692.
12. Andersen P, Gill R. Cox's regression model for counting processes: a large sample study. *Ann Statistics* 1982;10:1100–1120.
13. Pohjola S, Siltanen P, Romo M. Five-year survival of 728 patients after myocardial infarction: a community study. *Br Heart J* 1980;43:176–183.
14. Aspirin Myocardial Infarction Study Research Group. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;243:661–669.
15. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction: I. Mortality results. *JAMA* 1982;247: 1707–1714.
16. Furberg CD, Friedman LM, MacMahon SW. Women as participants in trials of the primary and secondary prevention of cardiovascular disease. Part II. Secondary prevention: the Beta-Blocker Heart Attack Trial and the Aspirin Myocardial Infarction Study. In: Eaker ED, Packard B, Wenger ND, et al., eds. *Coronary Heart Disease in Women*. New York: Haymarket Doyma; 1987:241–246.
17. Johansson S, Ulvenstam G, Vedin A, et al. Sex differences in postinfarction prognosis and secondary risk factors. In: Oliver MF, Vedin A, Wilhelmsson C, eds. *Myocardial Infarction in Women*. Edinburgh: Churchill Livingstone; 1986.
18. Oliver MF. Clinical characteristics and prognosis of angina and myocardial infarction in young women. In: Oliver MF, Vedin A, Wilhelmsson C, eds. *Myocardial Infarction in Women.* Edinburgh: Churchill Livingstone; 1986.
19. Gruchow HW, Anderson AJ, Barboriak JJ, et al. Postmenopausal use of estrogen and occlusion of coronary arteries. *Am Heart J* 1988;115:954–963.
20. 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.

21. Lan KKG, DeMets DL, Halperin M. More flexible sequential and nonsequential designs in long-term clinical trials. *Common Stat Theory & Method* 1984;13:2339–2354.
22. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–556.
23. Grady D, Gebretsadik T, Kerlikowske K, et al. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85:304–313.
24. Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. *Controlled Clin Trials* 1998;19:61–109.

APPENDIX

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