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Coronary Heart Disease in Women: Is There Any Role for Menopausal Hormone Therapy in Cardiac Protection?

BY NANETTE K. WENGER, MD, FACC, FAHA, MACP

Coronary heart disease (CHD) is the leading cause of mortality in American women. Clinical outcomes for women following both myocardial infarction (MI) and coronary artery bypass graft surgery (CABG) are less favorable than for men. These staggering statistics indicate that preventive interventions in women warrant major attention. Since CHD predominates in older women, consideration was raised whether hormones provided cardioprotection in younger women. A number of biologically plausible mechanisms, as well as a sizeable compendium of data from observational studies of hormone use, buttressed the interest in the potential for estrogen-mediated cardioprotection. However, the results of randomized, controlled, clinical trials of hormone therapy – both in healthy women and in those with established cardiovascular disease – failed to document evidence for cardiac protection, but rather, suggested harm. This issue of *Cardiology Rounds* reviews the data from these trials and examines their impact on contemporary clinical practice guidelines and federal regulatory decisions in the U.S.

Biologically plausible mechanisms for estrogen benefit¹

The longstanding interest in estrogen benefit derives from its overall advantageous effects on lipids and lipoproteins. Estrogen increases high-density lipoprotein cholesterol (HDL-C) by 10%-15% and comparably decreases low-density lipoprotein cholesterol (LDL-C).² Estrogen also decreases LDL-C oxidation, potentially limiting the adverse effects of oxidized LDL-C on vascular endothelium. Nonetheless, all oral estrogen preparations increase triglyceride concentrations.³

Despite its generally favorable effects on measures of coagulation and fibrinolysis, estrogen has been consistently associated with a small, but constant, increase in deep vein thrombosis (DVT) and pulmonary embolism, a conundrum that has yet to be resolved. Estrogen favorably affects levels of homocysteine, but all oral estrogen preparations increase levels of high sensitivity C-reactive protein (hsCRP),⁴ an independent predictor of coronary risk for both women and men. Estrogen lowers fasting glucose and insulin levels, decreases insulin resistance, and improves the distribution of body fat.^{3,5} Estrogen decreases the inflammatory response to atherosclerosis and vascular smooth muscle cell proliferation and promotes endothelium-dependent vasodilation.⁶ Given the complexity of the interplay between these factors, the biologic plausibility of estrogen benefit must be viewed as hypothesis-generating, rather than evidence for cardioprotection.

Observational study data

Meta-analyses of >30 epidemiologic studies have uniformly demonstrated a 35%-50% reduction in the risk of CHD with estrogen use and comparable benefits are evident in studies with combined estrogen plus progestin (Figures 1 and 2).⁷ Overall, cohort, angiographic, and case-control studies have all suggested substantial cardiac protection. Nonetheless, the pitfalls of observational studies include their selection biases – particularly important in menopausal hormone therapy – that may exaggerate benefits and underestimate risks. For example, healthy women with a favorable coronary risk profile are more likely to be prescribed hormone therapy. Additionally, there may be a compliance bias, which may be a marker for other nonmeasured healthy behaviors. If hormone use is discontinued due to early adverse effects, these women will not be captured as users in cross-sectional studies. The evidence for early adverse effects is subsequently addressed.



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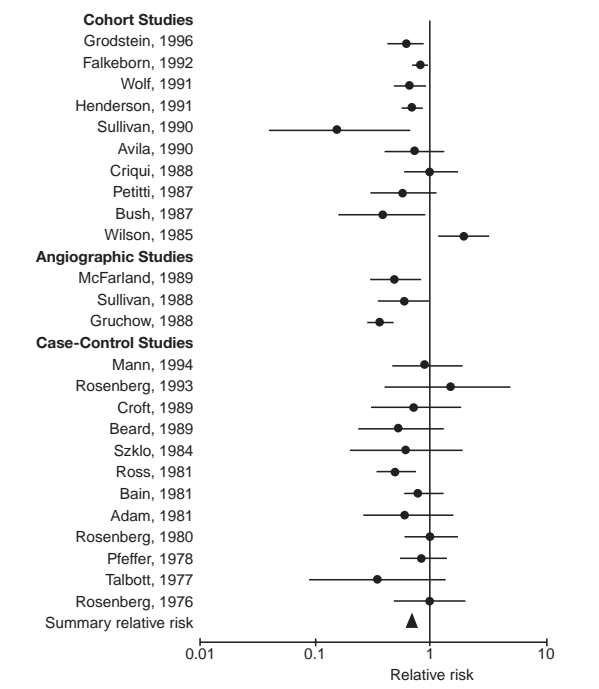
Brigham and Women's Hospital

Fax: (617) 732-5291 Website: www.heartdoc.org

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Figure 1: Risk for CHD in estrogen users compared to nonusers⁷



In 2002, the authors of a systematic review and meta-analysis of the observational studies cited above adjusted for socioeconomic status, educational levels, and major coronary risk factors.⁸ With these adjustments, the relative risk of cardiovascular disease was 1.07, indicating that even observational studies fail to support menopausal hormone therapy for the primary prevention of cardiovascular disease (CVD) and CHD.

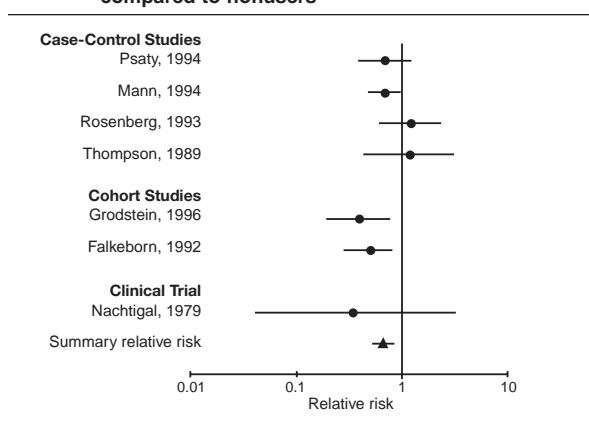
Noncardiac risks of menopausal hormone therapy

As a background to studies that will be subsequently cited, a 2- to 4-fold increase in the relative risk of venous thromboembolism with hormone use has been described in numerous research studies in recent years,⁹ although this risk was not prominent in earlier reports. More recent evidence demonstrates that there is a 40% increase in the occurrence of gallbladder disease requiring surgery associated with hormone therapy.¹⁰ Based on data from the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, unopposed estrogen use in women with an intact uterus is associated with a 10% annual incidence of abnormal or atypical endometrial hyperplasia.³ This cancer precursor is substantially decreased, but not totally obviated, by the use of added progestin. Finally, and of major concern to most women, is the 4- to 5-fold increased risk of breast cancer that has been described after >5-10 years of hormone use.¹¹ The prior concept that hormone-related breast cancer was associated with a more favorable prognosis has not been substantiated.

Randomized controlled clinical trial data The Heart and Estrogen/progestin Replacement Study (HERS)¹²

The first randomized placebo-controlled clinical trial data describing the cardiac outcomes of menopausal hormone therapy use was reported in 1998. HERS recruited 2763 menopausal women with an intact uterus, all of whom had documented CHD (eg, MI, prior surgical or mechanical revascularization, or at least 50% narrowing of a major coronary artery if

Figure 2: Risk for CHD in estrogen plus progestin users compared to nonusers⁷



the sole presentation was angina pectoris). Women up to age 80 years were randomized to receive 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate daily or an identical placebo.

By one year, and throughout the study, the anticipated changes in lipoprotein levels were noted. When compared with placebo, women receiving estrogen plus progestin had a greater decrease in LDL-C and a greater increase in HDL-C levels, with the unwanted, but anticipated, increase in triglyceride concentrations. Despite these generally favorable lipid effects, at the end of 4.1 years of follow-up, there was no difference in the relative hazard of total coronary events, the primary study endpoint, or in the subsets of coronary death and nonfatal MI. However, a post hoc analysis revealed an early increase in the risk of a coronary event (a relative hazard of 1.52 in the first year of the study) with hormone therapy and a later trend towards benefit.

Thus, this hormone regimen did not reduce overall coronary risk in women with established CHD and it was associated with a 3-fold increase in the risk of venous thromboembolic disease¹³ and a 40% increase in the risk of gallbladder disease requiring surgery. The HERS trial provided no data about unopposed estrogen effects, other estrogen/progestin regimens, or for women who did not have CHD.

Heart and Estrogen/progestin Replacement Study Follow-up (HERS II)¹⁴

To investigate whether the coronary risk reduction suggested during the later years of HERS persisted and resulted in an overall decrease in the risk of coronary events, HERS II, an open-label treatment and event surveillance trial, was conducted in 2321 women (93% of the survivors of HERS) for a mean of 2.7 years, extending the total mean observational period to 6.8 years.

Adherence to therapy decreased from 81% in the first year of the trial to 45% by year 6, although there was little increase in hormone use in the placebo group (0% in year 1, increasing to only 8% by year 6). Nonetheless, at trial end, no significant decrease in coronary events or in any secondary cardiovascular events was evident in the hormone versus placebo group, with a relative hazard for coronary events of 0.99 in HERS, 1.0 in HERS II, and 0.99 overall. Even after adjusting for potential confounders (eg, statin use), no difference was evident in the relative hazard, even in the subgroup of women who adhered to their randomized treatment assignment.

The conclusion of HERS investigators was that the lower rates of coronary events in hormone-treated women in the later years of HERS did not persist during additional follow-up, although almost half of the women originally assigned to estrogen plus progestin continued to take this therapy. This hormone regimen did not reduce the risk of any cardiovascular event – revascularization, unstable angina, heart failure, stroke, transient ischemic attack, peripheral arterial disease, etc. – in women with established CHD. Thus, this estrogen/progestin regimen should not be used to decrease the risk of cardiovascular events in women with CHD.

Papworth HRT Atherosclerosis Study (PHASE)¹⁵

This small randomized trial of transdermal hormone therapy in menopausal women with CHD (N=255) revealed no evidence for cardiac protection in the 134 women randomized to transdermal HRT. In fact, there was a nonsignificant increase in cardiovascular events in the hormone-treated women (with the event rate highest in the first 2 years) and a nonsignificant increase in the risk of venous thromboembolism each year.

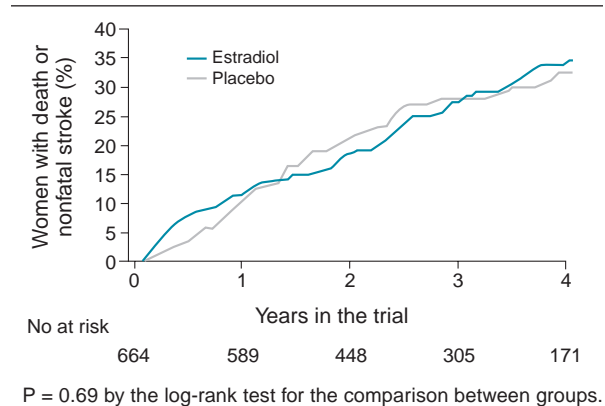
Estrogen Replacement and Atherosclerosis (ERA) Trial¹⁶

In this angiographic trial, 309 menopausal women with CHD were randomized to conjugated equine estrogen compared with placebo or conjugated equine estrogen plus medroxyprogesterone acetate compared with placebo, depending on hysterectomy status. At a mean follow-up of 3.2 years, no difference was evident in the angiographic progression or regression of coronary atherosclerosis. Results of this randomized trial differed markedly from observational angiographic data suggesting less coronary atherosclerosis in women using hormone therapy.

Women's Estrogen for Stroke Trial (WEST)¹⁷

The hypothesis of this randomized, double-blind, placebo-controlled trial was that daily estradiol would improve the outcome in menopausal women with a recent transient ischemic attack or ischemic stroke. Women (N=664) at a mean age of 71 years received 1 mg of 17β-estradiol daily compared with placebo. Estradiol did not decrease mortality risk (relative risk 1.2) or nonfatal stroke (relative risk 1.0) at a mean follow-up of 2.8 years. Rather, hormone-treated women had an increased risk of fatal stroke (relative risk 2.9) and those with nonfatal strokes had slightly worse neurologic and functional deficits, leading investigators to recommend that estradiol not be prescribed for the secondary prevention of cerebrovascular disease (Figure 3).

Figure 3: Kaplan-Meier curves for the time to the primary outcome (death or nonfatal stroke)



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Women's Health Initiative (WHI)

The Women's Health Initiative is the largest study ever conducted in menopausal women, involving approximately 160,000 women aged 50-79 years. The following discussion concerns the WHI randomized hormone trials, involving about 27,000 predominantly healthy women allocated to estrogen versus placebo or estrogen/progestin versus placebo based on hysterectomy status.

WHI Estrogen/progestin Study¹⁸

This study randomized 16,608 healthy women aged 50-59 years with an intact uterus to 0.625 mg of conjugated equine estrogen plus 2.5 mg of oral medroxyprogesterone daily or placebo, with the trial end planned for 2005. In 2002, however, after an average follow-up of 5.2 years, the Data Safety and Monitoring Board recommended early termination of estrogen plus progestin therapy for health safety concerns (ie, an increased risk of invasive breast cancer and an unfavorable pre-established global risk score). At that time, it was recommended that the parallel WHI trial of 0.625 mg of conjugated equine estrogen daily versus placebo in 10,729 women with hysterectomy continue.

The overall health risks of estrogen/progestin exceeded the benefits, with a 26% increased risk of invasive breast cancer, a 29% increased risk of coronary events, a 41% increase in stroke risk, and a doubled risk of venous thromboembolism. These risks contrasted with benefits, including a 37% decreased risk for colorectal cancer, a 33% decreased risk for hip fracture, and a 24% decreased risk for total fracture. All-cause mortality data were neutral (Figure 4).

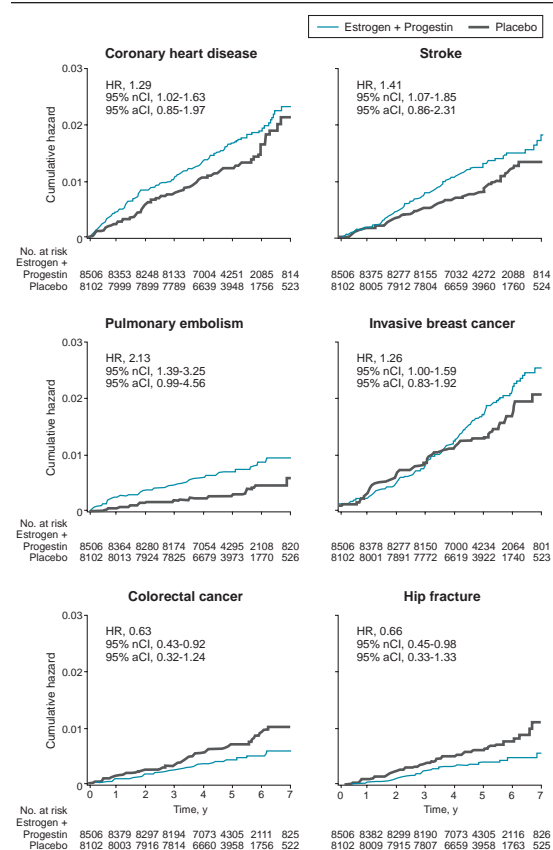
It is important to emphasize the low absolute excess risk of harm for an individual woman. However, although the risk of invasive breast cancer exceeded the preset trial stopping boundaries, it is relevant that breast cancer, coronary disease, stroke, and pulmonary embolism made approximately equal contributions to harm. For 10,000 such women treated for 1 year, there would be 7 more coronary events, 8 more strokes, 8 more pulmonary emboli, and 8 more cases of invasive breast cancer, in contrast to 6 fewer colorectal cancers and 5 fewer hip fractures. Despite the low absolute individual excess risk of harm, the population risk is substantial and, therefore, is not consistent with the requirements for primary prevention, ie, the preservation of health and the prevention of disease.

The WHI investigators concluded that there were no overall benefits with this hormone regimen. There was an excess risk of coronary events and stroke, with an 81% increased risk for MI during the first year of hormone therapy. Thus, this regimen was not recommended for initiation or for continuation in the primary prevention of CHD. A further analysis of the overall coronary data¹⁹ demonstrated that the hazard ratio for CHD was 1.24, with excess risk most apparent during the first year. Increased baseline levels of LDL-C were associated with greater CHD risk with hormone therapy, but baseline levels of C-reactive protein, fibrinogen, and other biomarkers did not significantly modify CHD risk with hormone therapy. Furthermore, the excess CHD risk was predominantly for MI, with no increase in risk for revascularization, angina pectoris, or heart failure.

WHI Memory Study (WHIMS)^{20,21}

Data from the estrogen/progestin arm of the WHI Memory Study were reported in 2003. This study involved 4,532 women, aged ≥65 years and free of probable dementia at baseline.

Figure 4: WHI Estrogen/Progestin Study – cumulative hazards for selected clinical outcomes



HR indicates hazard ratios; nCI, nominal confidence interval; and aCI, adjusted confidence interval.

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Although the absolute risk of developing dementia was small (for 10,000 such women treated with estrogen/progestin for 1 year, an additional 23 cases of dementia occurred), the risk of dementia in hormone-treated women was twice that in the placebo group (66% versus 34%). The increase in risk began to appear as early as the first year, with differences persisting over 5 years. Further, hormone therapy did not prevent mild cognitive impairment.

Global cognitive function was measured annually with a Modified Mini-Mental State Examination (mMMSE) in 4,381 women aged >65 years in the estrogen/progestin randomized trial. Although most did not experience clinically relevant alterations in cognition, a small percentage had substantial and clinically important declines in this test score. More hormone-treated women (6.7%) than placebo-treated women (4.8%) experienced a clinically important decline in the mMMSE.

WHI Estrogen Study²²

The estrogen-alone arm of the Women’s Health Initiative, involving 10,739 healthy women after hysterectomy, was discontinued in 2004 after an average follow-up of nearly 7 years due to lack of improvement in the pre-set global risk score. There was an increase in stroke risk similar to that seen in the estrogen/progestin arm, with 12 more strokes anticipated annually for every 10,000 women treated with 0.625 mg daily of conjugated equine estrogen. No increase or decrease in heart disease risk was evident.

There was a decrease in the risk of hip fracture, a non-significant decrease in breast cancer risk, and no decrease in the risk for colon cancer. Preliminary analysis of the Memory Study in the estrogen-only arm demonstrated a trend towards an increased risk of probable dementia and/or mild cognitive impairment in hormone-treated women.

Women’s Angiography Vitamin and Estrogen (WAVE) Trial²³

In this study, 420 menopausal women with at least one 15%-75% coronary stenosis on baseline angiogram were randomized to 0.625 mg of conjugated equine estrogen or 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (depending on hysterectomy status), and vitamins C plus E versus placebo in a 2 × 2 factorial design. After a mean follow-up of 2.8 years, there was nonsignificant worsening in the second coronary angiogram with both hormone therapy and vitamin treatment. There was an increased risk in clinical outcomes, death and nonfatal MI (p=.045) in the hormone-treated women and a suggestion of increased risk in the vitamin-treated women (p=.09). Thus, neither hormone therapy, nor antioxidant vitamins, provided cardiovascular benefit and a potential for harm was suggested with each treatment.

OEStrogen and the Prevention of ReInfarction Trial (ESPRIT)²⁴

This United Kingdom multicenter study of 1,017 menopausal women aged 50-69 years following a first MI, involved randomization to estradiol versus placebo for 2 years. At study end, there were no differences in the rates of reinfarction, cardiac death, or all-cause mortality. Of concern was the high percentage of noncompliance, with only 50% of estradiol-assigned women adherent to therapy, and 37% of placebo-assigned women taking hormone therapy by trial end.

Women’s Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELLHART)²⁵

This small trial of menopausal women with documented CHD involved a comparison between baseline and follow-up angiography at a mean of 3.3 years. Among the 226 women, (50% were diabetic and 70% were of racial or ethnic minorities), LDL-C levels were reduced to <130 mg/dL with a combination of diet and statin therapy. The women were randomized to 17β-estradiol, estradiol plus sequential medroxyprogesterone acetate, or placebo. There was no significant hormone effect on the angiographic progression of coronary atherosclerosis when added to lipid-lowering therapy. No increase in coronary events was evident during the first year, although the statistical power to detect this was limited.

Randomized controlled trial data: impact on clinical practice guidelines and regulatory requirements

American Heart Association Guidelines for Cardiovascular Disease Prevention in Women²⁶

These 2004 guidelines define menopausal hormone therapy as a Class III intervention, ie, lacking benefit and with the potential for harm. They indicate that combined estrogen plus progestin should not be initiated or continued to prevent cardiovascular disease in menopausal women. At the time of the report, it was recommended that other forms of menopausal hormone therapy (eg, unopposed

estrogen) should not be initiated or continued to prevent cardiovascular disease in menopausal women, pending the results of ongoing trials. This Level C recommendation (based on expert opinion) was changed by the results of the estrogen-only arm of WHI, released only weeks later, which elevated this Class III recommendation to a Level A – based on randomized controlled trial data.

U.S. Food and Drug Administration (FDA) Regulatory Requirements

In January 2003, the U.S. FDA required labeling changes for all estrogen and estrogen/progestin products. These changes were designed to help providers and patients balance the benefits and risks of such therapy.²⁷ It was emphasized that, in the U.S., menopausal hormone therapy was approved only for the vasomotor symptoms of menopause, for symptoms of vulvovaginal atrophy, and for the prevention of menopausal osteoporosis. These labeling changes highlighted an increased risk of heart disease, heart attack, stroke, and breast cancer. No change was recommended in the indications for moderate-to-severe vasomotor symptoms, except for guidance about using the lowest dose for the shortest period of time. It is noteworthy that none of the randomized trials cited above addressed hormone use for vasomotor symptoms; indeed, few women with severe vasomotor symptoms were enrolled in such studies, given the 50% likelihood of randomization to placebo therapy. For the treatment solely of symptoms of vulvovaginal atrophy, the FDA recommended that topical therapy be considered, since such therapy is not associated with significant blood levels of hormones. The FDA recommendation for the prevention of menopausal osteoporosis was to consider approved non-estrogen treatments, and hormone use only when the risks of osteoporosis outweighed the risks of estrogen use.

Women were advised to discuss ways to reduce heart disease risk factors and osteoporosis risk with their health-care providers. The FDA emphasized that research was needed for unanswered questions, specifically, the effects of lower-dose estrogens or progestins and other types of estrogens or progestins, and other methods of hormone administration (eg, transdermal), as potentially altering risk.

Based on the WHI Memory Study data, in February 2004, the FDA required a warning of the increased risk of probable dementia in women aged >65 years taking conjugated estrogen plus medroxyprogesterone acetate.²⁸ A further requirement, based on WHI data, was the identification that estrogen plus progestin therapy may increase the risk of an abnormal mammogram, which would lead to further evaluation. There was also a requirement for the manufacturer to specify the lowest effective hormone dose or state that the lowest effective dose of the hormone preparation has not been determined.

Has the last chapter been written on menopausal hormone therapy for cardioprotection?

The research requirements listed by the FDA warrant investigation to further explore the potential for cardioprotection and assess cardiovascular safety/risk for women using hormone therapy for menopausal symptoms. Among the pivotal questions is whether hormone therapy – initiated earlier in the menopause transition, the usual time when it is used to control menopausal symptoms – might provide

cardioprotection or lessen cardiovascular risk. These investigations should address different dosages,²⁹ formulations, and delivery mechanisms of menopausal hormone therapy. The role of selective estrogen receptor modulators also requires elucidation.^{30,31}

Of major importance in the initiation of these clinical trials will be consideration of safety issues, recalling the risks associated with conjugated equine estrogen plus medroxyprogesterone acetate in women with established CHD (in the HERS trial) and those associated with conjugated equine estrogen alone or with medroxyprogesterone acetate in healthy women (in the WHI randomized hormone trials). These issues pose challenges to industry, to women as potential participants in such clinical trials, and to the institutional review boards (IRBs) guiding these clinical trials. The first challenge will be the willingness and fiscal commitments of industry to undertake cardiovascular clinical endpoint trials or safety trials with already approved or evolving hormone therapies. Second, will be the decision of women to enroll in such trials, given their symptom profile and the information regarding potential risks from the published results of hormone clinical trials. Finally, for each individually designed trial, the IRBs will have to determine the relative scientific and ethical merits, balancing the importance and value of the resulting information for the common good of women against the safety of the individual participant.

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Nanette K. Wenger, M.D., M.A.C.P., F.A.C.C., F.A.H.A. is Professor of Medicine in the Division of Cardiology at the Emory University School of Medicine, Chief of Cardiology at Grady Memorial Hospital, and a Consultant to the Emory Heart and Vascular Center. Dr Wenger chaired the U.S. National Heart, Lung, and Blood Institute Conference on Cardiovascular Health and Disease in Women and the World Health Organization Expert Committee on Rehabilitation after Cardiovascular Disease. She has co-chaired the Guideline Panel on Cardiac Rehabilitation for the U.S. Agency for Health Care Policy and Research. Dr. Wenger is a Past President of the Society of Geriatric Cardiology and Editor of the *American Journal of Geriatric Cardiology*. Dr. Wenger received the Outstanding Professional Achievement Award from Hunter College in 1993, the President's Woman in Science Award of the American Medical Women's Association in 1993, and the Physician of the Year Award of the American Heart Association in 1998. In 1999, she received the Distinguished Achievement Award from the Scientific Councils of the American Heart Association and the American Heart Association's Women in Cardiology Mentoring Award and, in 2000, received the Shining Star Award for her distinguished career in cardiology and women's health issues. Dr. Wenger has also received the Elizabeth Blackwell Award and the James D. Bruce Memorial Award of the American College of Physicians for distinguished contributions in preventive medicine. In 2001, the American Heart Association presented her with the R. Bruce Logue Award for Excellence in Medicine and, in 2002, she received the Distinguished Fellow Award of the Society of Geriatric Cardiology. In 2004, Dr. Wenger received the Gold Heart Award, the highest award of the American Heart Association. She is listed in *Best Doctors in America*. Dr. Wenger has authored or coauthored over 1100 scientific and review articles and book chapters.



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