The increased incidence and prevalence of coronary heart disease among older women, coupled with the less favorable prognosis for women who sustain coronary events than for men, has resulted in the medical community’s attention to the potential beneficial effects of hormone therapy in menopausal women. Much biological evidence supports a protective mechanism of estrogen; nevertheless, some aspects are contradictory. Although observational studies have shown a clear cardiovascular benefit associated with hormone therapy, the significant skew inherent in these data has resulted in overestimation of benefits and underestimation of risks. Recent reanalysis of these observational data controlling for confounding variables failed to show cardiovascular benefit. Several randomized, double-blind, placebo-controlled studies have failed to show improvement in clinical cardiovascular outcomes with menopausal hormone therapy both in healthy women and in women with established coronary heart disease. Current research has also focused on pharmacologic agents that selectively modulate estrogen receptors, such as raloxifene, which are useful for the prevention and treatment of osteoporosis without increasing the risk of breast cancer. A clinical trial is now underway to evaluate the effects of raloxifene on coronary events and on the incidence of invasive breast cancer in menopausal women both with established coronary heart disease and at increased risk for coronary events. Current recommendations do not advocate the initiation of menopausal hormone therapy for the primary or secondary prevention of coronary events. The proven lifestyle interventions of smoking cessation, heart healthy diet, weight control, and physical activity should be undertaken, with statin use for control of elevated LDL cholesterol levels and pharmacologic blood pressure control when appropriate.

**Key words:** Estrogen. Coronary heart disease. Thromboembolism. Breast cancer. Raloxifene.
Heart disease is a significant cause of mortality in women (it is the leading cause of death in women in the United States); in addition, the prognosis after a myocardial infarction or coronary artery bypass surgery is significantly worse for women than for men. Thus there was considerable interest in any intervention that might provide cardioprotection and menopausal hormone therapy was explored in this regard.

**BIOLOGIC PLAUSIBILITY**

Biologic mechanisms suggesting benefit for estrogen are persuasive but at times contradictory. For example, estrogen has favorable effects on some lipid and lipoprotein concentrations, causing a 10% to 15% decrease in LDL cholesterol and a similar increase in HDL cholesterol levels. Nevertheless, oral estrogen therapy has a deleterious effect on triglyceride concentration. Estrogen also has a beneficial effect on many measures of coagulation and fibrinolysis, but paradoxically is uniformly associated with an increase in deep vein thrombosis and pulmonary embolism. In addition, although estrogen decreases homocysteine concentration, it elevates levels of the inflammatory marker C-reactive protein. Estrogen diminishes the inflammatory response to atherosclerosis, reduces the proliferation of vascular smooth muscle cells, and facilitates endothelial vasodilation; additionally, there is recent evidence that estrogens may enhance angiogenesis. However, biologic plausibility alone is only hypothesis – generating and is not evidence for cardiac protection.

**OBSERVATIONAL STUDIES**

Reports from observational studies almost uniformly identified that estrogen had a cardioprotective effect. A meta-analysis of these studies showed a 35% to 50% reduction in coronary risk associated with estrogen therapy; although there are fewer studies of the response to combination therapy using estrogen and progestin, these studies also suggest a beneficial effect. Observational data must be considered with caution, owing to factors that may distort the results of such studies.

Among these factors is the bias associated with the selection process. Women who smoke, are hypertensive, diabetic, obese, have angina, have heart failure, claudication, or those who have had a myocardial infarction or cerebrovascular accident were traditionally not considered candidates for menopausal hormone therapy. It is difficult to know to what degree the favorable results obtained are due to hormone therapy when the study population is selected for having few coronary risk factors or prior cardiovascular events. Another factor that influences results is treatment compliance. In several cardiovascular clinical trials, examination of both men and women in the placebo group showed that those adherent to placebo had a 40% to 60% lower occurrence of coronary events than those not adherent to placebo, obviously suggesting that adherence is a surrogate for other health-related behaviors. A third element that must be considered when interpreting the results of observational studies is the effect of early adverse effects. In a cross-sectional study, women who discontinued hormone use due to early the occurrence of adverse effects are not captured in the group of hormone users. Taking all these factors into account, observational data tend to overestimate benefits and underestimate risks.

A recent metaanalysis of the observational study data cited above that adjusted for socioeconomic status, education, and major coronary risk factors failed to demonstrate cardiac protection, with a relative risk of 1.07 for hormone users. This obviously reflects the fact that women who use hormone therapy differ from nonusers in many aspects including general health status, health consciousness, socioeconomic status, coronary risk attributes and the like. Additionally, a recently published scientific review for the U.S. Preventive Services Task Force examined both published observational and clinical trial data and summarized the effects of hormone therapy as follows: benefits included prevention of osteoporotic fractures and colorectal cancer; there was uncertainty as to the prevention of dementia; and harms included an increased risk of coronary heart disease, stroke, venous thromboembolism, cholecystitis, and breast cancer (with five or more years of hormone use).

**OUTCOMES FROM RANDOMIZED CLINICAL TRIALS**

The PEPI (Post-menopausal Estrogen Progestin Intervention) clinical trial was designed to study the effect of therapy with estrogen and progestin on cardiovascular risk factors in healthy menopausal women. The study hypothesis was that the administration of estrogen decreases the risk of coronary heart disease because of the favorable effect on cardiac risk factors. Healthy menopausal women were randomized to receive one of the following treatments: a) 0.625 mg daily of conjugated equine estrogen; b) the same estrogen dose combined with medroxyprogesterone acetate administered cyclically; c) the same dose of estrogen with medroxyprogesterone acetate administered continuously, and d) the same estrogen dose combined with micronized progesterone administered cyclically. These treatment groups were compared with a placebo group. The study showed a beneficial effect of all
hormone regimens on HDL cholesterol, LDL cholesterol, and fibrinogen concentrations, but an increase in triglyceride concentrations. The most favorable effect on HDL concentration was obtained with the administration of estrogen alone or with the combination of estrogen and micronized progesterone. The use of medroxyprogesterone acetate was associated with an increase in blood glucose levels, but none of the treatments had an effect on arterial blood pressure or insulin concentration. Similarly, none of the treatment regimens resulted in an increase in body weight compared with placebo. Significant adverse effects of estrogen were observed: in women who had a uterus and received unopposed estrogen, adenomatous or atypical endometrial hyperplasia (an unequivocal precursor of endometrial cancer) occurred at a rate of 10% annually. These data appropriately changed clinical practice, in that currently women with a uterus should receive estrogen associated with a progestin. The findings of the PEPI study show that estrogen administered in association with micronized progesterone is the best combination of the regimens studied for achieving a favorable coronary effect on HDL concentration was obtained (Fig. 1).

Nevertheless, at the end of the trial, there was no unwanted increase in triglyceride concentration with hormone therapy was also documented (Figure 1).

During follow-up, the changes in the lipoprotein profile occurred as anticipated; one year data showed a greater lowering of LDL cholesterol with estrogen/progestin than with placebo and concomitantly a greater increase in HDL cholesterol. The anticipated but increases in triglyceride concentration with hormone therapy was also documented (Figure 1).

revascularization, hospitalization due to unstable angina, hospitalization due to congestive heart failure, peripheral arterial disease, etc.).

What about clinical trial data subsequent to HERS? A small randomized study PHASE (the Papworth Hormone-replacement therapy Survival Enquiry) in

Fig. 1. Changes in the lipoprotein profile produced in the post-menopausal women included in the HERS study. As predicted, after 1 year of oral hormone therapy treatment there was a significant reduction in LDL concentration and an increase in HDL and blood triglyceride concentrations.
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the United Kingdom used transdermal hormone therapy compared with placebo in 255 menopausal women with coronary heart disease. The study was complicated by considerable therapeutic dropouts and drop-ins. At 4-year follow-up, a non-significant increase in cardiovascular risk, mostly early in the trial, and in venous thromboembolism was observed.\(^6\)

Early warning data were of concern in predominantly healthy menopausal women in the U.S. Women’s Health Initiative (WHI). This large study included more than 160 000 such women aged 50 to 79 years and explored various aspects of menopausal health, mainly in an observational cohort. In a subgroup of about 27 000 women, the researchers analyzed in a randomized, placebo-controlled trial, the effect of hormone therapy (estrogen alone in women who had undergone hysterectomy or estrogen with progesterone in women with an intact uterus) compared with placebo. In 2000, the Data Safety and Monitoring Board recommended that the investigators write each of the 27 000 women in the randomized trial informing them of an unexpected early increase in cardiovascular events (myocardial infarction and stroke) in both hormone groups compared with placebo; this was an unanticipated occurrence and the information was not included in the informed consent documents. This involved fewer than 1% of the women and, because of the possibility of late benefit, the Data Safety and Monitoring Board recommended continuation of the study. These events occurred in addition to the anticipated increase in venous thromboembolism. Again in 2001, the women were notified, at the behest of the Data Safety and Monitoring Board, that the small increased cardiovascular risk persisted in the year 3-4 data; again trial continuation was recommended.\(^6\)

The ERA (Estrogen Replacement and Atherosclerosis) study was an angiographic trial designed to investigate if hormone therapy (estrogen or estrogen plus progestin) was beneficial for the angiographic progression or regression of disease in women with documented coronary heart disease, as had been suggested by observational studies. An angiogram was performed at the initiation of the trial and at the end of an average of 3.1 years of follow-up. There were no differences in progression or regression of angiographic coronary heart disease. Once again, a hormone study was negative for benefit.

Two other intermediate outcome studies present contradictory data with regard to the benefit of hormone therapy on the progression of subclinical atherosclerosis. The German PHOREA (Postmenopausal HOrmone REplacement against Atherosclerosis) study analyzed the effect of estradiol combined with gestodene in women with an increased carotid artery intimal medial thickness by ultrasound examination. Although hormone treatment was associated with a significant decrease in LDL cholesterol, fibrinogen and FSH, there was no difference in the progression of subclinical atherosclerosis by carotid ultrasound at the conclusion of the study.\(^7\) On the other hand, the United States EPAT (Estrogen in the Prevention of Atherosclerosis Trial) study focused on the role of estradiol in healthy menopausal women with an LDL concentration >130 mg/dL. When the LDL value was >160 mg/dL, lipid lowering treatment was given. Women were followed by serial carotid ultrasound examination. At the end of this study, and in contrast to the results of the European study, there was a decrease in the progression of subclinical carotid atherosclerosis, but only in the women who did not receive statin therapy. Once statins were given, hormone therapy provided no additional benefit.\(^8\)

WEST (the Women’s Estrogen for Stroke Trial) investigated the role of 17-beta-estradiol in the prognosis of menopausal women (mean age, 71 years) who had a recent transient ischemic attack or ischemic stroke. Estrogen did not reduce the risk of death or non-fatal recurrent cerebrovascular accident, but increased the risk of fatal cerebrovascular accident and worsened the neurological signs and functional deficits that were a result of non-fatal stroke. The researchers concluded that estradiol is contraindicated for the secondary prevention of cerebrovascular disease.\(^9\)

Figures 2a and 2b, prepared in the spring of 2002, summarize the recent menopausal hormone secondary and primary prevention clinical trials, respectively, and the benefits and risks obtained from each. Both clinical outcome and intermediate outcome trials are presented.

**NEWLY REPORTED CLINICAL TRIALS: SUMMER OF 2002**

HERS II (the Heart and Estrogen/progestin Study follow-up)\(^10\) was an open label observational study that followed the majority of HERS participants for an additional 2.7 years, with women encouraged to remain on their original drug assignment. The question addressed was whether the trend toward a reduced risk of coronary events with hormone use in the later years of HERS would persist with additional follow-up. HERS II enrolled 93% of surviving HERS participants and about half of the women continued to adhere to their original study drug assignment. Nonetheless, with an average of 6.8 years of total follow-up, this estrogen/progestin regimen did not reduce the risk of cardiovascular events in women with established coronary heart disease. Even after adjustment for potential confounders, and other factors including statin use, there was no difference in outcome. Nor were outcomes altered when the analysis was performed.
on an «as treated» rather than the «intention-to-treat» basis. Given this null outcome, the concomitant risks deserve emphasis. There was a two-fold increase in the occurrence of venous thromboembolism, which predominated in the initial years; and a nearly 50% increase in the rate of gallbladder disease requiring surgery. Thus the investigators concluded that this estrogen/progestin regimen did not provide cardiovascular benefit for older women with established coronary heart disease and had the potential to cause harm.

The Women’s Health Initiative (WHI), on the advice of the Data Safety and Monitoring Board, terminated the estrogen/progestin therapy arm of the randomized hormone trial in July 2002, after an average follow-up of 5.2 years.¹¹ The therapy was terminated both because of an increased risk of invasive breast cancer that exceeded the preset trial stopping boundaries and because the global risk score showed an excess of harm over benefit. These women will continue to be followed on an observational basis. The estrogen-only arm of the randomized trial is continuing.

Because the overall benefit to risk ratio of estrogen/progestin for predominantly healthy menopausal women is unfavorable on a population basis, it cannot be recommended for health promotion and disease prevention. However, it is important to emphasize that the majority of women in WHI did not experience any adverse events, i.e., the individual risk of harm is small. For example, treatment of 2000 such women for 5 years with this combined hormone regimen would result in an excess of 7 coronary events, 8 strokes, 8 cases of invasive breast cancer, and 8 cases of pulmonary embolism; in contrast, there would be 6 fewer cases of colorectal cancer and 5 fewer hip fractures. It is worthy of note that coronary events, stroke, breast cancer, and pulmonary emboli contributed equally to harm.
the occurrence of hot flashes and leg cramps, that did not increase the rate of breast cancer but drastically reduced it (Taken from Cauley JA et al.13).
The scoring system used in RUTH was applied to analyze the osteoporotic women in the MORE study, to retrospectively identify those at increased risk of coronary events. Women at increased cardiovascular risk benefited significantly from raloxifene treatment with regard to the percentage of cardiovascular events that occurred during follow-up (Figure 5), which was not observed when the entire study population was analysed.16 Significantly, there was no early increase in cardiovascular events in increased cardiovascular risk MORE women treated with raloxifene.

**RECOMMENDATONS CONCERNING MENOPAUSAL HORMONE THERAPY FOR THE PREVENTION OF CARDIOVASCULAR DISEASE**

The 2001 recommendations of the American Heart Association (AHA)17 with regard to menopausal hormone therapy reflect the results obtained from recent clinical trials. Although prior coronary disease clinical practice guidelines of American College of Cardiology and the American Heart Association recommended hormone therapy as the preferred lipid reduction treatment for menopausal women with coronary heart disease, and these recommendations were also made by the National Cholesterol Education Program Adult Treatment Panel II (NCEP II), current guidelines advise administration of statins, which have been shown to provide a clear outcome advantage in clinical trials in women, without the risks association with hormone therapy. Current AHA recommendations are that initiation of hormone therapy is not indicated for the secondary prevention of coronary heart disease. In the 2001 AHA Scientific Advisory, in women with cardiovascular disease who had received hormone treatment for a prolonged period, the decision about whether to continue or interrupt therapy should be based on the established non-coronary benefits and risks of hormone therapy and patient preference. On the other hand, if a woman is hospitalized for an acute coronary event or other illness or surgery associated with immobilization while receiving hormone therapy, the risk of venous thromboembolism warrants interruption of treatment or venous thromboembolism prophylaxis is recommended.17

AHA clinical recommendations for use of hormone therapy for the primary prevention of coronary heart disease will derive from the results of clinical trials that are currently in progress. At present, there is insufficient evidence to recommend hormone therapy solely for the primary prevention of coronary heart disease; initiation and continuation of hormone therapy should be based, in healthy women, on the established non-coronary risks and benefits, on possible non-coronary risks and benefits, and on individual patient preference.

2002 AHA recommendations will be forthcoming. A recent U.S. National Institutes of Health publication18 presents a comprehensive evidence-based review of women’s health and menopause.

**REFERENCES**

5. Clarke S, Kelleher J, Lloyd-Jones H, Sharples L, Slack M,
Wenger NK. The Current State of Hormonal Prevention of Coronary Heart Disease in Menopausal Women


