Coronary heart disease is the single leading cause of death in women and a significant cause of disability. Menopause adversely affects several risk factors for coronary heart disease, suggesting that hormones influence the risk of coronary heart disease in postmenopausal women. This article reviews the observational and clinical trial data evaluating the relation between cardiovascular disease and hormone replacement therapy. Biological mechanisms of estrogen and the impact of adding progestins are emphasized. Potential risks and benefits of therapy are discussed. The relative effects of other estrogen and lipid-lowering therapies for preventing coronary heart disease in postmenopausal women are highlighted.

Cardiovascular disease (CVD) is the leading cause of death in the United States, accounting for approximately one half million deaths in women annually.1,2 More than half of these deaths are caused by coronary heart disease (CHD).1,2 Because of its earlier onset in men, CHD has been perceived to be a “male disease.” Women exhibit a steady increase in the incidence of CHD with age, and its occurrence is rare before menopause.3,4 The loss of endogenous estradiol production by the ovaries at menopause coupled with the increased risk of CHD associated with premature menopause suggests that estrogen replacement therapy (ERT) might reduce the risk of CHD in postmenopausal women.5

This article will address the recent evidence and the mechanisms for a possible role of unopposed ERT for the prevention of CHD. However, since estrogens are rarely used alone in postmenopausal women who have an intact uterus because of an increased risk of endometrial hyperplasia or cancer,6,7 the effect of adding progestins to estrogens—that is, hormone replacement therapy (HRT)—on the cardiovascular response will be emphasized. This is appropriate because 33% of women in the United States have undergone a hysterectomy by the age of 60 years.8 The noncardiovascular benefits and risks of HRT are briefly reviewed. Where necessary, the differences in responses to different doses, types, and regimens of replacement estrogens are noted. Finally, additional lipid-lowering therapies are compared with ERT/HRT.

RISK FACTORS FOR CHD AND THE ROLE OF ERT/HRT

Blood Lipids

Estrogen replacement therapy/HRT has been demonstrated to have a beneficial effect on several modifiable risk factors for CHD, including unfavorable lipid profiles. Elevated blood lipid levels are particularly important risk factors for the development of CHD in women.3-9 The Framingham Study5 demonstrated that total cholesterol levels increased after menopause in a cohort of 2873 women followed up since 1948. This increase was primarily due to an increase in low-density lipoprotein (LDL) cholesterol levels. There was also a slight decrease in high-density lipoprotein (HDL) cholesterol levels after menopause. Similar changes were reported in a cross-sectional study10 of 542 healthy, nonobese women 18 to 70 years of age. These alterations in blood lipid levels likely con-
tribute to the increased risk of CHD in postmenopausal women. A recent meta-analysis of 8 trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors concluded that reduction in the risk of mortality from CHD is proportional to the net reduction in total cholesterol levels. The cardioprotective effect of ERT/HRT in observational studies appears to be partly due to its ability to alter favorably the blood lipid profile. Several clinical studies have shown that ERT/HRT reduces plasma LDL levels. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, 875 healthy, postmenopausal women were studied using a randomized, double-blind protocol. The group receiving oral conjugated equine estrogen (CEE) (0.625 mg/d) had a 10% to 12% reduction in LDL levels during the 3 years of treatment. The addition of medroxyprogesterone acetate (MPA) or micronized progesterone to CEE did not affect this decrease in LDL levels. In a randomized, double-blind study designed to investigate the influence of estrogen dose on plasma lipids, 31 postmenopausal women were administered 2 dosages of CEE, 0.625 mg/d or 1.25 mg/d. Low-density lipoprotein cholesterol levels were reduced by 15% and 19%, respectively.

Differences between oral estrogen treatments in reducing LDL levels have been reported in some but not all studies. McManus and coworkers demonstrated a 13.8% (P<.01) decrease in LDL levels in postmenopausal women treated with CEE (0.625 mg/d), compared with 7.8% (P<.05) with estradiol valerate (1 mg) and 12.7% (P<.05) with estradiol (2 mg) and MPA (1 mg). No significant effect was seen with either estradiol (2 mg) and norethindrone (1 mg) or transdermal estradiol (50 µg). All doses were given once daily for 4 weeks. In a study among healthy, nonsmoking, postmenopausal women, LDL levels decreased by 15% (P<.001) in women treated with CEE (0.625 mg/d) for 3 months, compared with 14% (P<.005) with oral estradiol (2 mg/d). No effect was seen with transdermal estradiol (0.1 mg twice a week). In a more recent study, Egarter et al compared the effects of estradiol valerate (2 mg) and MPA (10 mg) with 0.625-mg CEE and 10-mg medroxyprogesterone and reported a significant decrease in LDL levels with estradiol valerate and MPA (P<.01) after 6 months but not with CEE. Because the doses of estradiol valerate and CEE used in the study are thought to produce an equal level of estrogenic activity, the difference in LDL reduction is likely the result of the dose and/or hormonal properties of the progestin components. Variations in the percentage of LDL reduction with ERT/HRT between studies are often because of the differences in baseline levels of LDL.

Beneficial reductions in LDL levels with the use of ERT/HRT are often accompanied by beneficial increases in the level of HDL. High-density lipoprotein facilitates the removal of cholesterol from extrahepatic tissues, and its levels are inversely associated with the risk of CHD, especially in women. In the PEPI trial, postmenopausal women assigned to treatment with unopposed CEE (0.625 mg/d) exhibited a 10% to 12% increase in HDL levels during the first 12 months of the study. The HDL level gradually decreased during the next 2 years but remained 7% above baseline at the conclusion of the study. The addition of MPA to CEE diminished but did not negate the beneficial alteration of HDL with HRT in the PEPI trial. In contrast, micronized progesterone did not significantly attenuate the HDL benefit associated with CEE. Thus, the magnitude of the decreased benefit may depend on the type, dose, and dosing regimen of the progestin used.

Studies that have examined treatment with other oral estrogens in addition to CEE have generally found similar increases in HDL levels. In a 3-month study by Walsh et al, CEE, 0.625 or 1.25 mg/d, increased HDL levels by 16% to 18%, while oral micronized estradiol, 2 mg/d, increased HDL levels by 15%; the increase in the HDL level was because of an increase in the HDL2 fraction. Transdermal estradiol (0.1 mg twice a week) had no effect. Twenty-two healthy, hysterectomized, postmenopausal women who were treated with oral estradiol valerate (1 mg/d), CEE (0.625 mg/d), or transdermal estradiol (50 µg/d) for 4 weeks in a crossover design study had a 7.1% increase in HDL levels with estradiol valerate (P<.01) and a 6.3% increase with CEE (P<.05) at the end of treatment but no significant change (P>.05) with transdermal estradiol. In a substudy conducted by these authors and reported in the same article, among 18 healthy, nonhysterectomized, postmenopausal women, estradiol (2 mg/d) combined with norethisterone (1 mg/d) significantly lowered HDL levels after 4 weeks. When estradiol was combined with MPA (5 mg/d), it produced a nonsignificant decrease (P>.05) in HDL levels. The reduced effect on HDL levels of transdermal estradiol is because of its minimal effect on hepatic metabolism since it bypasses the portal circulation, although Pornel reported that CEE and transdermal estradiol had equally positive effects on total cholesterol and HDL levels.

A third beneficial effect of ERT/HRT is the reduction of lipoprotein(a) [Lp(a)]. Lipoprotein(a) is a complex of an LDL-like particle and apolipoprotein A (apoA). Elevations in Lp(a) have been associated with CHD and thrombotic stroke. The mechanism of this relationship is not known, but it is thought that because apoA and plasminogen are homologous, elevated levels of Lp(a) may interfere with fibrinolysis and therefore promote thrombosis. Estrogen replacement therapy/HRT appears to favorably alter Lp(a) levels. In a randomized, double-blind, crossover study of 100 women who had undergone hysterectomies, 6 months of oral estradiol (2 mg/d) reduced Lp(a) levels by nearly 10%. After 12 months, no further decrease was reported. Shewmon et al reported a 24% decrease in Lp(a) levels in postmenopausal women receiving CEE (0.625 mg/d) for 2 months, and Lobo et al reported a 32% decrease in Lp(a) levels after 6 months of treatment with CEE (0.625 mg/d) in women who had surgical menopause. In contrast, transdermal estradiol (50 µg/24 hours, twice a week) reduced Lp(a) levels by approximately 10%. Data from the PEPI trial indicated that
Several studies have shown that the use of ERT/HRT results in an increase in triglyceride (TG) levels, which may also be associated with CHD risk and mortality. For example, Austin et al analyzed population-based prospective studies 12,13,15,17 of 5 of the subjects involving women, and found a statistically significant increase in the risk of incident CVD of 14% in men and 37% in women, when adjusted for HDL-C level and other risk factors. Bass et al followed up 1405 postmenopausal women for an average of 14 years and reported a strong correlation between TG levels and death due to CVD. Triglyceride levels greater than 4.50 mmol/L (398 mg/dL) were associated with a more than 3-fold increase in the risk of CVD mortality. Manolio et al also found a significant association (P < .05) of TG levels with risk of CHD in 5 of 6 cohort studies of middle-aged women younger than 65 years; however, the studies’ statistical power was not adequate to determine whether the TG level was an independent risk factor.

In a randomized, double-blind, crossover study, Walsh et al observed that estradiol benzoate reduced the incidence of atherosclerotic lesions in the coronary arteries of cholesterol-fed chicks without affecting aortic atherogenesis. In cholesterol-fed female rabbits, 17β-estradiol reduced both the severity of aortic atheromas and the cholesterol content of the lesions. The combination of 17β-estradiol and levonorgestrel was as effective as 17β-estradiol alone in reducing aortic cholesterol accumulation in ovariectomized, cholesterol-fed rabbits. These authors noted that the reduction in aortic cholesterol accumulation with 17β-estradiol plus norethisterone acetate was less dramatic compared with the effects of 17β-estradiol alone or 17β-estradiol plus levonorgestrel. The antiatherogenic activity of estrogen has been observed in some primate models. In ovariectomized, cholesterol-fed cynomolgus monkeys, subcutaneously administered 17β-estradiol and oral CEE reduced coronary artery plaque area by 50% and 72%, respectively. The influence of progestins added to estrogens in this model is unclear and may depend on the drug used, the route of administration, and the dosing regimen. In one study, cyclically administered progesterone (28 days on, 28 days off) delivered subcutaneously did not influence the estradiol-induced reduction in plaque area, whereas continuous oral administration of MPA inhibited the beneficial action of oral CEE. Likewise, Adams et al found that continuous oral administration of MPA antagonized the protective effect of CEE on aortic atherosclerosis. In contrast, Williams et al reported that neither CEE nor CEE plus MPA augmented the beneficial effect of a lipid-lowering diet on the regression of established coronary atherosclerotic lesions in surgically postmenopausal cynomolgus monkeys.

The Estrogen Replacement and Atherosclerosis (ERA) study, the first randomized clinical trial to examine the effect of ERT/HRT on the progression of coronary atherosclerosis in women, was recently completed. In 309 women with existing CHD, there was no benefit of CEE, 0.625 mg/d, alone or in combination with MPA, 2.5 mg/d, on slowing the progression of coronary atherosclerosis, based on quantitative angiography, compared with placebo after 3.2 years of follow-up. In a 10-year nonrandomized angiographic study of 2268 women with coronary artery disease (CAD), the difference in survival of women with stenotic lesions was highly significant (P = .007) when ERT users were compared with never users. These data suggest long-term therapy with ERT may prevent progression; however, selection bias may also have contributed to the observed benefit. In postmenopausal women who participated in the Asymptomatic Carotid Atherosclerotic Progression Study (ACAPS), ERT use was associated with the cessation and potentially with the reversal of the progression of carotid artery atherosclerosis as assessed by ultrasonography.

A possible antiatherogenic activity of estrogen may be mediated by its ability to inhibit the hydrolysis of cholesterol ester or by its ability to reduce the susceptibility of LDL and HDL to oxidation in the vessel wall. However, the results of more recent clinical studies have been conflicting. Wakatsuki et al reported that CEE (0.625 mg/d) reduced the oxidation of LDL and HDL in postmenopausal women. In a randomized, crossover study, O’Sullivan and colleagues compared the effects of CEE (1.25 mg) and transdermal estradiol (100 µg/24 hours) on lipid oxidation in 18 postmenopausal women. Conjugated equine estrogen but not transdermal estradiol had significant (P > .05) antioxidant activity. Additionally, a recent clinical trial found that the addition of a progestin to CEE reversed its antioxidant effect. In contrast, McManus et al observed that CEE (0.625 mg/d), transdermal estradiol (50 µg/24 h), and...
oral estradiol (estradiol valerate, 1 mg/d) did not affect LDL oxidation in postmenopausal women. Reasons for these differences are not readily apparent. 46

Vascular Effects

Estrogen and progestin receptors are present in the vasculature. Estrogen has been reported to restore normal vasodilation responses to acetylcholine in coronary arteries of postmenopausal women, a response consistent with increasing endothelial nitric oxide production. 47,48 For example, in a study of 33 postmenopausal women with stable angina, atypical chest pain, or an abnormal exercise electrocardiogram (ECG), intravenous ethinyl estradiol (35 µg) increased mean ± SD coronary blood flow by 23% ± 4% and decreased mean ± SD coronary vascular resistance by 15% ± 3%. Placebo treatment had no effect. In 7 of these patients, intracoronary acetylcholine caused a reduction in mean ± SD coronary blood flow (assessed by Doppler ultrasonography) of 34% ± 12%, a response indicative of abnormal endothelium. After administration of intravenous estradiol, a small increase in blood flow in response to acetylcholine was reported. It should be noted that these doses may be greater than the equivalent estrogen dose administered long term in hormonal replacement regimens. In a similar study, 49 transdermal estradiol (100 µg/24 hours) not only blocked the vasoconstrictor response to acetylcholine but actually reversed it.

Studies 50-53 have also evaluated the effect of estrogens, with or without progestins, on peripheral arterial blood flow. In women who had undergone a hysterectomy, 6 months of HRT use with either oral estradiol (2 mg/d) or estradiol (2 mg/d) plus cyclical MPA (5 mg/d) increased blood flow velocity in the arteries at the wrist and ankle. 50 Bush et al 51 investigated posts ischemic vasodilation of the brachial artery using Doppler ultrasonography in postmenopausal women who received either oral CEE (0.625 mg/d) or CEE plus MPA. Mean ± SD posts ischemic vasodilation increased by 5% ± 7% after 1 month and increased further (overall, 8% ± 3%) after 6 months of either treatment. Women with the greatest endothelial dysfunction at baseline demonstrated the greatest improvement. Administration of transdermal estradiol (0.2 mg/d) alone or in combination with vaginal micronized progesterone (300 mg/d) increased brachial artery diameter more than twice as much as placebo following reactive hyperemia in postmenopausal women. 52 In a study of postmenopausal women with CAD, Herrington et al 53 reported that HRT with and without lowestatin increased brachial artery flow–mediated vasodilator capacity; the increase was greatest with HRT alone.

Increases in brachial arterial blood flow following reactive hyperemia were also noted in postmenopausal women receiving CEE (0.625 mg/d) plus MPA (2.5 mg/d) but not estradiol (2 mg/d) plus norethindrone acetate (1 mg/d). 54 Sorensen et al 55 also reported no difference in forearm blood flow during reactive hyperemia in women treated with sequential estradiol and progesterone (2-mg/d estradiol for 12 days, 2-mg/d estradiol plus 1-mg/d norethisterone for 10 days, and 1-mg/d estradiol for 6 days) for 2.1 to 4.3 years, compared with the untreated control group. In contrast, Sullivan et al 56 found that neither oral CEE (0.625 mg/d for 21 days) nor intravenous CEE (25 mg) affected forearm blood flow, and the addition of oral MPA (10 mg/d) for 10 days significantly (P = .004) increased forearm vascular resistance. The dose of MPA administered by Sullivan et al 56 was double that used in other studies, 57 in which no effect on peripheral blood flow of the added progestin was noted. Estrogen has also been reported to stimulate endothelial production of prostacyclin, 58 a potent vasodilator as well as an inhibitor of platelet aggregation.

Novel Risk Factors

The potential role of ERT/HRT on plasma viscosity, an established predictor of CVD events, was recently investigated. 57 After 3 months of treatment with either estradiol (1 mg/d) alone or estradiol plus MPA (2.5 mg/d), plasma viscosity, measured with a coaxial microviscometer, was reduced by 4%, compared with a 3.3% increase for the control group. However, only the decrease in plasma viscosity of the ERT group was significantly (P < .01) different from the placebo group. Other putative mechanisms for the antiatherogenic effects of estrogen include down-regulation of inflammatory cell adhesion molecules, interference with cytokine and growth factors, reduction of vascular smooth muscle cell migration and proliferation, and inhibition of extracellular matrix formation. The data in support of these mechanisms are conflicting and have been recently reviewed. 59 It should be noted that ERT/HRT has been shown to increase levels of C-reactive protein, a novel risk factor for CHD. 60 The clinical relevance of alterations in this inflammatory marker on clinical events has not been established.

Smoking

Because of its potentially beneficial effects on endothelial function, lipid oxidation, and atherosclerosis, it has been suggested that the use of postmenopausal hormone therapy may be of particular benefit to postmenopausal smokers. 61 Initial research has been conducted in a cross-sectional study of arterial structure, function, and plasma lipid levels in 140 age-matched, postmenopausal smokers and nonsmokers. 62 Investigators found that smokers using HRT, compared with smokers not using therapy, had lower cholesterol levels and more favorable mean values for carotid artery intima-media thickness and systematic arterial compliance, 2 surrogate markers of vascular disease. 63 Additional randomized clinical studies with larger sample sizes are necessary to evaluate the interaction between the effects of HRT and smoking on cardiovascular disease.

ERT/HRT AND CHD EVENTS

Observational Studies

More than 30 epidemiological studies of the association between CHD
and ERT/HRT in postmenopausal women have been reported. These studies have consistently shown a reduction in the incidence of CHD\textsuperscript{62,63} and in the overall mortality\textsuperscript{64} of postmenopausal women using ERT/HRT.\textsuperscript{65-69} In an early report on the Nurses’ Health Study\textsuperscript{70} cohort, for example, more than 32,000 postmenopausal women who were initially free of CHD were followed up at 2 and 4 years. Women who were currently using ERT had a relative risk (RR) of 0.30 (95% confidence interval [CI], 0.14-0.64; \(P = .002\)) for a nonfatal myocardial infarction (MI) and fatal CHD compared with women who had never used ERT. Ever users, that is, women who had used ERT in the past but who were not current users, had an RR of 0.59 (95% CI, 0.33-1.06), although this was not statistically significant (\(P = .08\)). The type of ERT most frequently used by the participants was unopposed oral CEE; very few women used HRT. In a 16-year follow-up of the Nurses’ Health Study cohort, Grodstein et al\textsuperscript{71} reported similar beneficial effects. Among current users of ERT, the multivariate-adjusted RR for major CHD was 0.60 (95% CI, 0.43-0.83); for postmenopausal women who were currently using HRT, the adjusted RR was 0.39 (95% CI, 0.19-0.78). A similar beneficial effect of ERT/HRT use on CHD death was observed for the 41,837 participants in the Iowa Women’s Health Study.\textsuperscript{72} The RR of CHD death with ERT/HRT use was reduced in women with (RR, 0.56; 95% CI, 0.30-1.04) or without (RR, 0.71; 95% CI, 0.57-0.89) a family history of breast cancer. In a Swedish cohort study, Falkeborn et al\textsuperscript{73} observed 23,174 postmenopausal women for an average of 5.8 years. They reported that in women who were younger than 60 years old at the onset of the study, oral CEE or estradiol reduced the incidence of a first MI by 31% compared with never users (RR, 0.69; 95% CI, 0.54-0.86). Estradiol combined with levonorgestrel also resulted in a reduction in the risk for a first MI (RR, 0.52; 95% CI, 0.30-0.87). The cardioprotective effect did not extend to women prescribed estrogen compounds. Other studies\textsuperscript{64,67,71} have supported a cardioprotective role for ERT/HRT.

Meta-analyses of these studies\textsuperscript{5,74} suggest that ERT reduces the risk of CHD by 35% to 50%; fewer studies\textsuperscript{75} have evaluated the cardioprotective effect of HRT, but these have likewise reported beneficial effects.

It has been suggested, however, that epidemiological studies may overestimate the amount of protection attributed to estrogen.\textsuperscript{1} This may be because of prescription, prevention, or compliance bias as well as differences in socioeconomic status and education.\textsuperscript{75,76} A “healthy woman selection bias” was recently documented in a prospective investigation, the Healthy Women’s Study,\textsuperscript{77} which followed up 355 menopausal women through menopause. Thus, only randomized clinical trials can confirm the direct benefit of ERT/HRT for protecting women from CHD.

Clinical Trials

Data from clinical trials that have evaluated the effect of HRT on CHD are limited. A recent analysis\textsuperscript{78} of the impact of postmenopausal HRT on cardiovascular events in 23 trials, mostly involving healthy women, did not support a protective effect. The odds ratio (OR) of cardiovascular and thromboembolic events in users of HRT was 1.64 (95% CI, 0.65-4.18) compared with nonusers. The nonusers’ variability in lengths of treatment and regimens used and inconsistency in the data described for cardiovascular events prevented the authors from conducting a formal meta-analysis. The study’s methods and conclusions were questioned in several letters to the editor.\textsuperscript{70-83} In addition to using data from short-term trials designed to study outcomes other than CVD and cancers, only 7 of the 23 trials reported any cardiovascular or thromboembolic events.\textsuperscript{80} When Col et al\textsuperscript{83} repeated the analysis with the at-risk group limited to those studies that specifically noted the presence or absence of cardiovascular events, they found an RR of 0.65 (95% CI, 0.18-2.32) for CHD events in users of HRT. Additional randomized studies that are currently under way, including the Women’s Health Initiative (WHI) randomized trial\textsuperscript{84} and the Women’s International Study of Long-Duration Oestrogen After Menopause (WISDOM)\textsuperscript{85} trials, will help to clarify the effect of HRT for the primary prevention of CHD events.

Only one large-scale, randomized, double-blind, placebo-controlled trial of secondary prevention has been conducted to date. Results from the Heart and Estrogen/Progestin Replacement Study (HERS),\textsuperscript{16} a multicenter, prospective study of 2763 postmenopausal women with established CHD and an intact uterus, were recently reported. There were no differences between the treatment (oral dose CEE, 0.625 mg/d, plus MPA, 2.5 mg/d) and placebo groups for the primary end point, which was the occurrence of nonfatal MI or CHD death. However, a statistically significant time trend (\(P = .009\)) was noted, with more CHD events occurring during year 1 in the hormone group compared with the placebo group, but fewer events in years 4 and 5. These findings led the authors to conclude that women with existing CHD should not begin HRT but that it could be appropriate for women already receiving hormone therapy to continue to use it. Based on the results of the HERS trial, a consensus panel of the American Heart Association and the American College of Cardiology\textsuperscript{86} has suggested that initiation or continuation of HRT be considered in women for whom the potential benefits of therapy may exceed the potential risks. The panel recommended that the decision be individualized based on a woman’s history of heart disease and risk factors for CVD as well as the risk of thromboembolic disease, gallbladder disease, osteoporosis, breast cancer, or other health risks.

A pattern of early, transient increase in risk of CHD events with hormone treatment, followed by a significant decline over time, is supported by preliminary data from the Nurses’ Health Study.\textsuperscript{87} Previous cohort studies have also supported a cardioprotective effect in long-term users of HRT.\textsuperscript{88,89}

Reasons for the troubling initial increase in recurrent CHD events are not known, although an increase in thromboses, inflamm-
tion, arrhythmias, or ischemia with HRT use is possible among a susceptible subgroup of women with existing CHD. The study’s authors suggest that the use of MPA might have played a role in increasing the risk of CHD events by blunting the beneficial increase in HDL levels, an effect observed in the PEPI trial. Clinical trials that have compared the effects of MPA with those of other synthetic progestins, however, have shown that MPA results in higher or similar HDL levels. However, the PEPI trial demonstrated that micronized progesterone did not mitigate the beneficial HDL-raising effect of CEE in contrast to MPA. Whether the type of progestin used or its regimen of use was a significant factor in the study’s results requires further study.

It has been suggested that the apparent early thrombotic risk might have been attenuated by a lower dose of estrogen at the initiation of therapy. The HERS trial investigators did not report if a specific subgroup of participants was most subject to the early risk of CHD events. It has been suggested that if older participants (those without physiologic hormone levels for 2 or more decades) had been given a lower dose of HRT for the first 6 months of treatment, the early risk might have been reduced. The possibility that lower doses of estrogen may preserve an antiatherogenic benefit without increasing thrombotic events is an attractive hypothesis. The mechanism of action behind the early rise, however, still needs to be identified.

As the authors of the HERS trial point out, longer studies with a broader range of participants may provide more definitive results about HRT and secondary CHD protection. The results of the HERS trial may not apply to women using unopposed estrogens or different regimens of HRT as well as those women without CHD. The average age of the women with heart disease enrolled in the study was 66.7 years; thus, the results may not be generalizable to postmenopausal women who are younger or without documented CHD. Further studies of the secondary prevention effects of HRT use in postmenopausal women are the Western Connecticut Estrogen for Prevention of Stroke Trial (WEST) and the Estrogen in the Prevention of Reinfarction Trial (ESPRIT). Studies of women with atherosclerosis include the ERA trial, the Women’s Atherosclerosis Vitamin/Estradiol (WAVE) trial, and the Women’s Estrogen/Progestin and Lipid Lowering Heart Atherosclerosis Trial (WELL-HART). These 3 trials are limited to angiographic end points but should provide further evidence of the early events in HRT users in the aggregate.

Noncardiovascular Benefits of ERT/HRT

Hormone replacement therapy relieves vasomotor and urogenital symptoms associated with estrogen deficiency during menopause and prevents osteoporosis. Osteoporosis is prevented because estrogens increase bone mineral density by decreasing bone resorption and loss, thereby potentially decreasing the incidence of osteoporotic fracture. More recently, ERT has been shown to prevent or delay the onset of Alzheimer disease. Estrogen replacement therapy improves cognitive function, alleviates symptoms of dementia, and increases regional cerebral blood flow. Furthermore, improved cognitive function and a lower rate of ischemic brain damage are associated with ERT use in postmenopausal women. Other reported benefits of ERT/HRT use include an improved quality of life, lowered RR of death and a reduced risk of colorectal cancer.

Noncardiovascular Risks of ERT/HRT

Replacement estrogens have been associated with an increase in endometrial cancer, thromboembolic events, and possibly breast cancer. The potential link between estrogen use and endometrial cancer is well known. More than 35 epidemiological studies have documented that unopposed estrogen use increases the risk of endometrial cancer about 4-fold and that this risk increases with the duration of therapy. However, epidemiological studies also show that the addition of progestins to estrogens eliminates or even decreases this risk.

The potentially adverse relationship between oral contraceptives and venous thromboembolism (VTE) is well documented. Several epidemiological studies have investigated the relationship between HRT use and VTE risk, including pulmonary embolism. Using a population-based, case-control model to study 347,253 women aged 50 to 79 years, Perez Gutthann et al reported that current users of HRT had a 2-fold increased risk of VTE and that the increase was not dependent on the dose, route of administration, or addition of progestins. The increased risk was confined to the first year of treatment among current users. In a smaller case-control study, Daly et al found a 3.5-fold increased risk of VTE in current users of HRT and a similar lack of influence of the dose, route of administration, or addition of progestins. Data from the Nurses’ Health Study indicated that current HRT users had an RR for primary pulmonary embolism of 2.1 (95% CI, 1.2–3.8) compared with postmenopausal women who had never used HRT. However, these authors noted that the absolute risk of primary pulmonary embolism was small (68 cases per 633,817 person-years of follow-up). Increased VTE risk with HRT use has also been reported in the HERS trial of postmenopausal women with existing CHD. Of interest is that in some but not all of these studies, an inverse relationship exists between the duration of use of HRT and the RR for VTE; the risk was greatest in short-term users (<1 year). This observation has not been fully explained but may be the result of perimenopausal use of HRT. At the onset of menopause, estrogen production occurs at a reduced but erratic rate. The use of HRT in this setting may result in higher-than-expected estrogen levels, leading to an increased incidence of VTE. There may also be a subset of women who are at higher risk for VTE because of genetic predisposition, such as Leiden Factor V or because of a coexisting disease condition, such as diabetes mellitus. Nonetheless, idio-
pathic VTE is a rare event in women older than 50 years, occurring in only 1 in 10,000.94

More than 70 epidemiological studies have been conducted to determine whether an association between HRT use and breast cancer exists.121 In a recent meta-analysis, the Collaborative Group on Hormonal Factors in Breast Cancer122 reanalyzed data from 51 studies of women from 21 countries. These authors reported an increased incidence of breast cancer with current use of HRT of 0.2% after 5 years of use, 0.6% after 10 years, and 1.2% after 15 years. This increase was confined to localized disease, which may be indicative of enhanced surveillance. A meta-analysis by Grady et al123 of nearly 40 studies indicated that there were inconsistent results—RRs ranged from 0.2 to 1.9 for women who had ever used HRT compared with nonusers.

Recent data from the Iowa Women’s Health Study,124 a population-based cohort study that followed up a cohort of 37,105 postmenopausal women at risk for developing breast cancer, found a positive, dose-dependent association between duration of hormone use and the incidence of breast cancer with a favorable prognosis. Breast cancer defined as having a “good” histologic profile was seen only in 5% of the study population, however, and the risk of other types of breast cancer, for example, ductal carcinoma in situ, was not increased. Hormone replacement therapy was not associated with an increased risk in either short-term (≤5 years) or long-term (>5 years) users when all tumor types were combined and stratified by duration of use.124 In an extended follow-up of the Nurses’ Health Study,125 the RR for breast cancer was 1.3 to 1.4 (P < .05) among current users of HRT with or without progesterins. Similarly, the RR was 1.30 for users of HRT in the HERS trial, although this result was not statistically significant (P = .33).16

In summary, no clear consensus has emerged regarding the association between the use of HRT and breast cancer risk.121 However, clinicians should be aware that the lifetime risk of death from atherosclerotic disease is approximately 10 times that from breast cancer.9 Moreover, in healthy women aged 50 years and older, CHD causes 3 times as many deaths as osteoporotic fracture, breast cancer, and endometrial cancer combined.52

**ERT/HRT and Other Pharmacotherapy for Prevention of CHD in Postmenopausal Women**

**Statins**

Currently, the most effective therapies for lowering LDL levels are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins.11,126 These drugs block the synthesis of cholesterol in the liver, which results in a decrease in plasma LDL levels. A meta-analysis of 8 clinical trials documented the beneficial effect of statins for reducing CHD events in men and women through exerting dramatic reductions in total serum cholesterol levels.11 Investigators concluded that the risk of mortality from CHD is proportional to the net reduction in total cholesterol.

The use of statins is reported in clinical trials to reduce LDL levels in postmenopausal women with hypercholesterolemia by 25.4% to 45%.8,55,126-129 In trials that compared statins with ERT/HRT, decreases of LDL levels averaged 15.9 percentage points higher with statins than with CEE or HRT.8,55,128,129 Triglyceride levels also declined significantly with statins, decreasing by as much as 33% in one recent randomized, crossover trial that compared simvastatin (20 mg/d) with HRT.120 However, ERT/HRT produced equal or higher increases in HDL levels than statins. In a recent trial13 of 76 postmenopausal women with hypercholesterolemia, 19 of whom were treated with CEE (0.625 mg/d) for 16 weeks, HDL levels increased by 22.5%. In the same trial, pravastatin sodium produced an HDL increase of only 3.7%. In 2 trials that measured Lp(a), levels fell by 23% (0.625-mg/d CEE plus 2.5-mg/d MPA)129 and by 27% (up to 1.25-mg/d CEE plus 5-mg/d MPA)128 with HRT, while simvastatin produced no measurable result.

The combination of statins and HRT may have a more beneficial effect on the overall lipid profile than either alone. In the most recent randomized, double-blind trial using combined treatment, 24 postmenopausal women with CAD and hypercholesterolemia were treated with HRT (oral dose of 0.625-mg/d CEE plus 2.5-mg/d MPA) combined with lovastatin (20 mg/d) for 6 weeks.55 Combined treatment produced a greater decrease in LDL levels and a greater increase in HDL levels than either treatment alone and effectively abolished the increase in TG levels associated with the onset of menopause. No significant adverse effects of the combined treatment were reported. Similar results were seen in other trials, with combined treatment being well tolerated.8,129 It is not known if the more favorable lipid profile resulting from the combination of HRT and statins will translate into a synergistic clinical benefit.

**Selective Estrogen Receptor Modulators**

Selective estrogen receptor modulators (SERMs) have been proposed for the management of postmenopausal health.130 These drugs are reported to block the effect of estrogens in the reproductive tissues but may have estrogenic effects in other tissues of the body (eg, bones and heart).130 With respect to CHD, SERMs have been shown to reduce LDL levels with no significant change in HDL or TG levels in postmenopausal women. In a 24-month study131 of 140 postmenopausal patients with breast cancer, tamoxifen (10 mg twice a day) reduced LDL levels by 20% without a persistent and significant decrease in HDL levels. The decrease in LDL levels persisted during a 5-year follow-up of a subgroup of these patients.132 Similar reductions in LDL levels have been reported with raloxifene.133-135 Lipoprotein(a) levels are also decreased by tamoxifen26 and raloxifene,137 and the response to tamoxifen26 appears to be greater than that seen with CEE.136 Fibrinogen levels may also be lowered to a larger degree by SERMs than by HRT.133,136
The results of preclinical studies with SERMs suggest smaller cardiovascular effects than those seen with HRT. In ovariectomized, cholesterol-fed rabbits, raloxifene inhibited the aortic accumulation of cholesterol by 33% compared with the control group, an effect half as large as that seen with 17β-estradiol. In ovariectomized monkeys, tamoxifen reduced coronary artery atherosclerosis but without a corresponding decrease in cholesterol levels. In contrast, in a similar model, raloxifene reduced plasma LDL levels but had no significant effect on coronary artery plaque size.

In a recent meta-analysis of adjuvant tamoxifen trials in 37,000 women with breast cancer, no significant reduction in CVD mortality was observed. The generalizability of this results to women at risk for CHD is not known. Ongoing trials, such as the Raloxifene Use for the Heart (RUTH) trial, will determine the clinical impact of SERMs in women at risk for CHD.

CONCLUSION

The use of ERT and HRT has been associated with improved cardiovascular risk factors and surrogate end points in postmenopausal women. The results of epidemiological studies in women free of CVD are consistent with a cardioprotective effect. Beneficial effects on lipoproteins and nonlipid parameters both contribute substantially to the biological plausibility of these findings. However, data from randomized clinical trials in women with existing CHD do not support a role of HRT to prevent the progression of disease or recurrence of cardiovascular events. More data are needed to elucidate mechanisms associated with the increased risk of cardiovascular events in some women. Findings from randomized trials currently under way will be useful for providing definitive conclusions regarding long-term use of HRT in the primary prevention of CHD. Currently, the use of ERT/HRT for the treatment of menopausal symptoms is indicated. The decision to use ERT/HRT for the prevention of heart disease should be individualized and made in the context of other health risks affected by hormones.

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Corresponding author: Lori Mosca, MD, PhD, Preventive Cardiology, New York-Presbyterian Hospital, PH 10-203D, 622 W 168th St, New York, NY 10032 (e-mail: ljm10@columbia.edu).

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