Coronary artery disease (CAD) is the number 1 cause of death and disability in the Western world. The incidence of CAD increases with age, although, on average, women present with symptomatic CAD about 10 years later than men. The belief that hormone replacement therapy (HRT) may reduce the incidence of CAD is based on its favorable effects on (1) vasoreactivity, (2) progression of atherosclerosis, (3) lipids and lipoproteins, (4) hemostasis, and (5) impaired glucose tolerance. However, unopposed estrogen may be related to an increased risk of endometrial cancer. The belief that HRT has an overall beneficial effect on cardiovascular disease comes from the results of prospective cohort studies. The Heart and Estrogen/progestin Replacement Study (HERS), however, showed no beneficial effect of HRT on cardiovascular morbidity and mortality. Uncertainty exists about the duration and optimal type of HRT regimen to use, because different estrogens and progestins have yielded different results. Results of ongoing trials addressing similar questions will be published in future years. The Women’s Hormone Intervention Secondary Prevention (WHISP) pilot study, using a different HRT regimen from that used in HERS, will assess the effect of HRT on lipid and hemostatic risk markers of heart disease, and it may provide the rationale for a large trial evaluating the effect of HRT on morbidity and mortality. ©2002 by Excerpta Medica, Inc.

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EFFECTS OF HORMONE REPLACEMENT THERAPY ON THE CARDIOVASCULAR SYSTEM

There are many potential benefits of HRT, in particular, estrogen, on the cardiovascular system, including antiatherogenic and vasodilatory actions. Interests, other hormones, and related substances including testosterone, raloxifene, and plant-derived estrogens, have also been shown to have vascular activity.

Experimental studies have demonstrated that continuous conjugated equine estrogens (CEE) augment endothelium-mediated dilation and delay progression of atherosclerosis in animal models. Infusion of physiologic doses of 17β-estradiol in women with CAD during cardiac catheterization has been shown to increase coronary blood flow in response to acetylcholine. The role of endogenous ovarian hormones in modulating peripheral vasoreactivity has been investigated in premenopausal women.

Endothelium-dependent vasodilation induced by hyperemia varies significantly during the menstrual cycle and is dependent on serum estradiol concentration. This suggests that ovarian hormones, at physiologic concentrations, have effects on vasomotor tone, and it confirms similar findings with estrogen treatment. Estrogen increases flow-mediated vasodilation in the brachial artery of postmenopausal women, which implies that endothelium-dependent responses in the peripheral circulation may be modulated by steroid hormones. Some of the short-term, rapid effects of estrogen that have been demonstrated can now be explained by recently discovered rapid nongenomic but plasma membrane estrogen receptor–dependent actions via cytosolic signaling systems, such as the mitogen-activated protein kinase cascade.

Data on the vascular actions of progestins are scant, less clear, and more complex, because the ef-
Effects of the interaction with estrogen must be taken into account. Progesterone relaxes coronary arteries in a dose-dependent manner. The relaxing potencies of the different progestins in coronary arteries vary and depend on whether the vessel has been exposed to estrogen. A complex relation thus exists between estrogens and progestins with regard to vascular reactivity. Measurements of endothelial function in response to different progestins in healthy women have produced varying results. Studies suggest that results may differ depending on the specific estrogen and progestin investigated.

HORMONES AND EXERCISE-INDUCED MYOCARDIAL ISCHEMIA

Because of estrogen’s relaxing effects in vitro and in animals and its actions on vascular reactivity and coronary blood flow in humans, the potential beneficial effects of estrogen on myocardial ischemia have been investigated. Rosano et al showed that 17β-estradiol has anti-ischemic effects in postmenopausal women with CAD. This effect was confirmed by Alpaslan et al using a different methodology. A double-blind, randomized, placebo-controlled study conducted by Webb et al demonstrated that 4 and 8 weeks of transdermal estradiol therapy significantly increased exercise time to myocardial ischemia. When the effects of natural progesterone were compared with those of medroxyprogesterone acetate (MPA), a beneficial effect of oral estradiol combined with transvaginal progesterone on exercise time to myocardial ischemia in menopausal women with CAD was demonstrated. In contrast, oral estrogen plus MPA did not produce a significant improvement over estrogen alone. Results of these studies suggest that the choice of progestin combined with estrogen in women with CAD may be important. Estrogen administered on a short-term basis was shown, with the use of coronary sinus pH measurement, to have an acute anti-ischemic action in menopausal women with CAD.

In summary, data from a variety of studies have provided strong evidence that estrogen and some progestins can act as anti-myocardial ischemic agents in menopausal women with proven CAD. Further studies are required to show whether estrogen alone or combined with progesterone has long-term beneficial effects in such women.

FIGURE 1. Incidence of chronic diseases in relation to age in women. Approximately 12% of US women, 45 to 64 years of age, exhibit clinical evidence of coronary artery disease; this number increases to 33% in women ≥65 years of age. (Reprinted with permission from BMJ.)

MENOPAUSE, CARDIOVASCULAR DISEASE, AND RATIONALE FOR FURTHER STUDIES

Cardiovascular disease rarely affects women before menopause, which strongly implicates estrogen deficiency in its etiology. Data from the Nurses’ Health Study have shown that the risk of CAD among women who had bilateral oophorectomy before menopause is more than double the risk among women of a similar age who did not. Investigators, in a review of population-based, case-control, cross-sectional, and prospective studies of estrogen therapy (with most using CEE) and CAD, calculated that estrogen use reduces the overall relative risk of CAD by approximately 50%.
Observational studies comparing current hormone users with nonusers have shown consistent reductions in CAD risk of 35% to 50%. A recent, updated report of the Nurses’ Health Study noted that the risk reduction (relative risk, 0.61; 95% confidence interval, 0.52 to 0.71) was seen with the most commonly used dose of CEE (0.625 mg/day); there appeared to be a similar risk reduction at the lower dose of 0.3 mg/day (relative risk, 0.58; 95% confidence interval, 0.37 to 0.92). The findings from observational studies have been important in promoting the belief that HRT prevents CAD. However, there may be potential bias in these studies, although the findings from a large number of them are very consistent.27

With the exception of the pooled data from a number of small, short-term studies, the clinical trials of HRT and CAD have all been in the area of secondary prevention. Studies of men with CAD who were given higher doses of estrogen were stopped early for safety reasons after a higher rate of cardiovascular events was found in the treatment group than in the control group.28 In the Heart and Estrogen/progestin Replacement Study (HERS), women assigned to daily estradiol and norethisterone acetate showed an improvement in variables related to CAD risk,29 but no difference was found between the groups.30 The first placebo-controlled angiographic trial of CEE or CEE plus MPA also failed to show benefit in women with CAD.31 According to a preliminary report of a randomized trial, transdermal estrogen and progestin also failed to show benefit in patients with CAD.32

There are a number of possible explanations for the null results of the clinical trials of HRT in subjects with or at risk of CAD. First, it is possible that there may be an early prothrombotic effect of oral conjugated estrogen in susceptible subjects. An association has been shown between the use of HRT and myocardial infarction in menopausal hypertensive women with the prothrombin 20210G→A variant. Confirmation of this finding in other studies may allow better risk assessment associated with HRT in women.33

Another possibility is that the progestin used, namely MPA, negated the potential beneficial effect of estrogen early in the study. Biologic support for this possibility comes from reports that show a detrimental effect of MPA on the beneficial effects of CEE in vascular reactivity34,35 and atheroma development.36,37 Studies also show that progesterone does not appear to have this inhibitory effect, either on atheroma development38 or vascular reactivity in animal models.39 or on vascular reactivity40 and exercise-induced myocardial ischemia in humans.23 Progestins, such as norethisterone, have more potent relaxant actions than other progestins in vitro.15

Norethisterone enhances rather than inhibits the effects of estrogen on atheroma development in animal models of atherosclerosis.7

Before clear decisions about the cardioprotective role of HRT can be made, clinical trials of different estrogens at different doses and with different combinations of progestins must be conducted to determine if their effects differ. For instance, transdermal estrogen may have less thrombogenic potential than oral estrogen, although lower doses of oral estrogen may also prove to be less thrombogenic. There is also uncertainty about the duration of treatment and the optimal HRT preparation that should be used. Vascular remodeling may also be affected. Estrogens increase matrix metalloproteinase activity in a dose-dependent manner.41,42 Matrix metalloproteinases are responsible for the degradation of extracellular matrix components, such as collagen and proteoglycans, and have been implicated in the development of CAD.43 Evidence also indicates that they may contribute significantly to atheromatous plaque rupture43 and may well be involved in plaque progression and regression.

Clinically, it is difficult to know which is the most appropriate progestin for the cardiovascular system. In a recent long-term study, micronized progesterone added to estradiol did not attenuate the favorable effect of estradiol on endothelium-dependent vasodilation in postmenopausal women,40 whereas MPA did attenuate this effect in another study.17 Similarly, women treated with gonadotropin-releasing hormone agonists who were given “add-back” continuous oral estradiol and norethisterone acetate showed an improvement in flow-mediated brachial artery reactivity compared with women who did not receive HRT.18

These results indicate the need for further research into the issue of HRT in older women who have documented CAD or are at increased risk of vascular disease. Further randomized studies investigating different estrogens, progestins, doses, routes of administration, and patient populations are required before definitive conclusions can be made about HRT and cardioprotection.

ONGOING STUDIES OF HORMONE REPLACEMENT THERAPY AND MAJOR CLINICAL OUTCOMES

Several randomized studies of HRT are in progress.44 The Women’s Health Initiative (WHI), conducted by the National Institutes of Health in the United States, is randomizing approximately 30,000 women to either combined continuous estrogen (0.625 mg CEE) and progestogen (MPA) or placebo (women who have had a hysterectomy receive estrogen alone or placebo) to evaluate the impact of HRT in the primary prevention of CAD.45 After a 2-year interim analysis, the WHI Safety Monitoring Committee recently issued a warning that there was a small increase in vascular events with HRT during the early part of the study. However, this increase must have reversed subsequently, as the study has not been curtailed on safety grounds. Furthermore, the overall incidence of vascular events in the study thus far was reportedly

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lower than that seen in the background population. No valid comment on the WHI outcomes can be made until this trial has been completed and the data have been scientifically analyzed and subjected to peer review.

The Medical Research Council’s Women’s International Study of Long Duration Estrogen after Menopause (WISDOM) is a large primary prevention study in which 34,000 postmenopausal women (22,000 from the United Kingdom), 50 to 69 years of age, will be randomized to either the HRT group or the control group. Results of both WHI and WISDOM are not expected to be reported within the next 5 years.

The Estrogen in the Prevention of Reinfarction Trial (ESPRIT) has randomized 1,017 women, 50 to 69 years of age after their first myocardial infarction, to address the effects of estradiol valerate 2 mg/day or placebo on death or recurrent myocardial infarction. Recruitment began in 1996 with the intention to enroll 2,000 women. The women will be observed for 2 years, and the findings should be reported after February 2002. ESPRIT excludes women >69 years of age, who are at higher risk of major cardiovascular events and make up a large proportion of admissions for myocardial infarction. There are also concerns, as noted above, about the safety of using unopposed estrogens in postmenopausal women who have not undergone hysterectomy.

RATIONALE FOR A STUDY OF HORMONE REPLACEMENT THERAPY AFTER ACUTE MYOCARDIAL INFARCTION

A research program designed to provide reliable evidence of safety and tolerability of HRT in postmenopausal women after myocardial infarction (which will further help to formulate public health policy about this treatment) is being undertaken with the support of the United Kingdom Medical Research Council.

The Women’s Hormone Intervention Secondary Prevention (WHISP) program is investigating the effects of continuous combined HRT in 125 postmenopausal women (with no upper age limit) between 48 hours and 28 days after the onset of acute myocardial infarction or acute coronary syndrome. Women entering the study will be randomly allocated in double-blind fashion to either continuous combined oral HRT (17β-estradiol 1 mg and norethisterone acetate 0.5 mg) or placebo. Follow-up study will occur at 3, 6, 9, and 12 months, with a minimum follow-up interval of 6 months.

The use of continuous combined HRT should avoid the cyclical withdrawal bleeding associated with sequential HRT and thus be more acceptable to older women. The use of a low dose of estradiol should reduce the incidence of estrogenic side effects (e.g., breast tenderness and fluid retention) and also circumvent the potential hazards of increased matrix metalloproteinase activity and minimize any increases in thrombogenesis. The use of norethisterone acetate should reduce the incidence of any adverse progestogenic effects on estrogen-induced vascular changes.

In this pilot study, a sample size of 125 patients would have 96% power to detect a difference of 0.3 mmol/L in levels of low-density lipoprotein between treated patients and control subjects after 3 months of treatment, assuming a standard deviation of 0.4 mmol/L and an α of 0.05. These assumptions have been based on differences in levels of low-density lipoprotein observed in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, in which decreases in levels of low-density lipoprotein in the treatment groups ranged from 0.37 to 0.46 mmol/L over 3 years, compared with placebo.

The main objectives of the pilot study are to assess the tolerability of HRT and the feasibility of enrolling patients in a randomized, placebo-controlled trial of HRT in the post–myocardial infarction setting. The rates of admission of eligible patients, enrollment, compliance, and side effects will be recorded, and the effects on lipid profiles and hemostatic factors will be evaluated. Clinical events (including death, reinfarction, and hospital readmission), net costs, and quality of life will be also be assessed.

SUMMARY AND CONCLUSION

CAD is the major cause of morbidity and mortality in men and women. Estrogen has been shown consistently to favorably influence endothelial dysfunction, lipid profile, and hemostatic factors related to CAD risk. The evidence that HRT may be beneficial in reducing cardiovascular risk in postmenopausal women is derived from large epidemiologic studies. However, robust evidence from randomized, placebo-controlled trials that HRT is of benefit in either primary or secondary prevention of major cardiovascular events is currently lacking.


