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CARDIOLOGY Rounds™

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After HERS: What is the role of HRT in the prevention of CAD in women?

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Background

Cardiovascular disease—coronary artery disease (CAD), cerebrovascular disease, and aneurysm—remains the leading cause of death in women in North America, accounting for 45% of all deaths in females in the U.S. in 1994.[1] One in two North American women will eventually die of coronary artery disease or stroke, whereas 1 in 25 will die of breast cancer.[1] The mortality rates for CAD in the U.S. have been decreasing since 1979; however the rate of decline is less for women than men.[2] Despite this reduction, the aging of the population has led to an actual increase in female cardiovascular deaths.[3] The prognosis for women with diagnosed CAD is worse than for men, with significantly greater mortality. Thus, great emphasis needs to be given to the prevention of CAD in women.

Premenopausal women have much lower rates of CAD in comparison to men. However, after menopause these rates increase and then approximate those of men, so that by the sixth decade the incidence of CAD is similar in both men and women.[4] Menopause as a result of bilateral ovariectomy is also associated with an increased risk of CAD. Observational studies have suggested, but cannot prove, that estrogen replacement therapy is associated with lower CAD risk.[5] The American College of Physicians has recommended that all postmenopausal women be considered for estrogen replacement therapy;[6] however the evidence supporting the use of hormone replacement therapy (estrogens + progestins) for the prevention of CAD in postmenopausal women remains unproven by prospective randomized clinical trials. The recently published Heart and Estrogen/progestin Replacement Study (HERS) failed to establish that estrogen replacement therapy in postmenopausal women with CAD reduces MI and cardiac death. This was the first randomized prospective study of estrogen replacement therapy and was notably negative with respect to the study hypothesis.

Proposed mechanisms of benefit

The seeming connection between hormone replacement therapy (HRT) and lower CAD risk has generated the hypothesis that estrogen exerts cardioprotective effects; however, the mechanisms underlying these purported beneficial effects are still unclear.

Effect on lipoprotein profile

The best-characterized and accepted cardioprotective effect of estrogens is that of modulation of the serum lipid profile. After menopause, low-density lipoprotein (LDL) cholesterol and lipoprotein(a) levels rise, and high-density lipoprotein (HDL) cholesterol levels fall, resulting in a more atherogenic lipid profile.[7,8] Estrogen replacement therapy leads to a reduction of LDL by 15–20%, elevation of HDL by 15–20% and a decrease in lipoprotein(a) of about 15%. Other observed changes include an elevation of triglycerides of about 25%, and a rise in very-low-density lipoprotein (VLDL) cholesterol of about 30%,[9–14] as well as a reduction in LDL oxidation suggesting an antioxidant effect.

There remains concern that progestins might attenuate the cardioprotective effects of estrogen. The effects of progestins on the lipoprotein profile vary depending on the androgenicity of the progestin. The more androgenic progestins (e.g., levonorgestrel and norethindrone) are associated with lower

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HDL cholesterol levels than the less androgenic ones (e.g., medroxyprogesterone acetate and micronized progesterone).[15]

The premiere study addressing the effects of hormone replacement therapy on lipoprotein profile is the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.[16] This randomized, double-blinded, placebo-controlled trial studied the effects of commonly-used HRT regimens on CAD risk factors: HDL cholesterol (and LDL), fibrinogen, blood pressure, and serum insulin. The study enrolled 875 postmenopausal women into either the placebo arm or one of four separate treatment arms: unopposed estrogen, continuous estrogen with cyclical progestin, continuous estrogen and continuous progestin, or estrogen plus micronized progesterone. In comparison with placebo, each active treatment regimen was associated with a significant increase in HDL cholesterol. The increase was greatest in those receiving unopposed estrogens followed closely by those receiving estrogen and micronized progesterone. However, LDL decreased significantly and equally in all active treatment groups, regardless of the presence of progestins. Triglyceride levels increased comparably and significantly in all active treatment groups compared to placebo.

The Lipid Research Clinics Program Follow-up Study demonstrated that only 25–50% of the beneficial effect of estrogen could be attributed to changes in lipid profile.[17] Similarly, in the Atherosclerosis Risk in Communities Studies,[12] the estimated reduction in CAD risk secondary to alteration of metabolic factors including lipids was 42%. These studies suggest that effects in addition to beneficial changes in lipid profile contribute to the reduction in CAD risk with hormone replacement therapy in postmenopausal women.

Effects of estrogen on the vasculature

The endothelial monolayer performs important functions: anti-atherogenic, antithrombotic, and vasodilatory. Thus, preservation of endothelial function is important for preserving vascular health. Several studies have demonstrated that estrogen might preserve endothelial function. Animal studies have demonstrated a potentiation of endothelium-dependent vasodilation of both femoral and coronary arteries of ovariectomized animals by estrogen administration.[18,19] Similar effects of acetylcholine-induced vasodilation (acetylcholine causes endothelium-dependent vasodilation) have been shown in the forearm and coronary vascular beds in postmenopausal women.[20] Reis et al[21] showed an attenuation in acetylcholine-induced vasoconstriction of epicardial coronary arteries (a paradoxical response seen in atherosclerotic coronary arteries and signifying endothelial dysfunction) by intravenous ethinyl estradiol. Similar effects of intracoronary 17-beta estradiol have been shown in female but not male atherosclerotic coronary arteries.[22] This suggests that the immediate effects of estrogen might be receptor-mediated, as estrogen receptors have been identified in female coronary arteries. Inhibitors of nitric oxide synthase such as L-NMMA have been shown to block the effects of estrogen on acetylcholine-mediated increase in coronary blood flow, suggesting that this effect is mediated in part at least by increased nitric oxide generation.[23]

Other effects of estrogen on the vasculature include the attenuation of vasoconstrictor responses to endothelin-1 and norepinephrine, a direct non-endothelium–dependent vasodilatory effect especially at supraphysiologic doses[24] by effects on ion channels including calcium channels[25] and ATP-dependent potassium channels, and effects on stimulating angiogenesis possibly via growth factors such as fibroblast growth factor (FGF) and vascular endothelium growth factor (VEGF) or more directly via nitric oxide.

Effects on hemostatic factors

More recent studies have demonstrated favorable effects of estrogen use on the balance of fibrinolysis/thrombosis. In the Atherosclerosis Risk in Communities Study[12] and the PEPI trial,[16] users of estrogen at current lower doses (alone or in combination with progestins) had lower plasma levels of fibrinogen than non-users. Other potentially beneficial effects on hemostatic factors include reduced plasminogen activator inhibitor (PAI-1) levels and increased tissue plasminogen activator (tPA) levels. The effects of high-dose estrogen supplementation on coagulation factors have been a concern given the thrombotic complications (such as deep-vein thrombosis) associated with its use in the past. However, studies of women taking contemporary doses of estrogen therapy have reported favorable effects of hemostatic factors.

Other effects of HRT

Evidence from the PEPI Trial[16] suggests little benefit of HRT on blood pressure (either systolic or diastolic), or on fasting or 2-hour insulin levels. Other proposed favorable effects of estrogen include decreased platelet activation, reduced collagen and elastin synthesis, and reduced smooth-muscle cell proliferation.

Clinical trials of HRT

Virtually all the epidemiologic evidence to date is from observational studies. Three study designs have been predominantly used:

- case-controlled studies comparing estrogen use in women with CAD and those without CAD,
- cohort studies comparing rates of CAD among women taking estrogen with those not taking estrogen,
- cross-sectional studies of women undergoing angiography comparing the extent of CAD in estrogen users and non-users.

The majority of studies have looked at the effects of estrogen replacement therapy on cardiovascular events and on all-cause mortality. Ten out of 13 case-controlled studies showed a risk reduction in cardiovascular events in those who received estrogen replacement therapy, but only one reached statistical significance. In contrast, 16 out of 17 prospective cohort studies showed a significant protective effect of estrogen therapy.[26–29]

Table 1: Angiographic studies of estrogen replacement therapy and coronary artery disease

Author	Relative risk	N	Design	End point	P
Sullivan[30] (1988)	0.40	2,188	case-control	≥70% stenosis	0.002
Gruchow[31] (1988)	0.59	933	cross-sectional	moderate-to-severe stenosis	< 0.01
Mcfarland[32] (1989)	0.50	345	case-control	≥70% stenosis	< 0.01
Hong[33] (1992)	0.13	90	cross-sectional	≥25% stenosis	< 0.001

Four cross-sectional angiographic studies have examined the effect of estrogen replacement therapy on the degree and extent of coronary atherosclerosis (table 1). All 4 studies showed significantly less coronary atherosclerosis in women who used estrogen therapy. Follow-up from the study by Sullivan et al.[30] looked at the effect of estrogen replacement on all-cause mortality in postmenopausal women whose coronary status had been determined by coronary angiograms.[29] Women without CAD at baseline had good survival rates regardless of use of estrogen replacement. In contrast, women with CAD at baseline who used estrogens had significantly better survival rates. The difference between users and non-users was greatest in those with severe CAD: 60% survival in non-users as compared to 97% in the users over 10 years (P=0.07). In addition, when other risk factors were corrected for, estrogen was found to have a significant effect on survival.

A meta-analysis by Grodstein and Stampfer[28] combining all 3 types of studies, and comparing users (both current and previous) of estrogen versus non-users, yielded a summary relative risk of 0.64 (95% CI, 0.59–0.68). However, when they further examined the evidence from many of the studies, current estrogen users seemed to have greater protection against heart disease than past users. On recalculation of summary estimates based on analyses of current use, where such data was provided, the combined relative risk for current estrogen users versus non-users was 0.50 (95% CI, 0.45–0.59) or a relative risk reduction of 50%.

The clinical data addressing the issue of combined hormone replacement therapy (estrogen and progestin) and reduction in CAD is less strong (table 2).[35-40] In women with an intact uterus, progestins are often prescribed along with estrogens to eliminate the risk of excess endometrial cancer caused by unopposed estrogen. In the only published randomized clinical trial of hormone replacement therapy, that of Nachtigall et al.,[34] 168 women were randomized to treatment with estrogen and medroxyprogesterone acetate or placebo. The relative risk of myocardial infarction was reduced to 0.33. However, due to low numbers of patients, this did not reach statistical significance. Recently, the latest follow-up of the Nurses' Health Study[40] was published. This prospective study began in 1976 and has followed a large cohort of female registered nurses. Follow-up data on 59,337 women over 16 years showed that the relative risk for major coronary heart disease was 0.39 (95% CI, 0.19–0.78) in women who used combined hormone replacement therapy as compared to those who did not receive hormone replacement therapy. The relative risk in those women on estrogen replacement therapy alone was 0.60 (95% CI, 0.43–0.83). As well, 3,637 deaths from 1976 to 1994 were documented. Once adjustments for confounding variables were made, the relative risk of death was 0.63 (95% CI, 0.56–0.70) for current hormone users as compared to those women who never used hormones. However, with use greater than 10 years this benefit seemed to decrease with a relative risk of 0.80 (95% CI, 0.67–0.96). Women with coronary risk factors appeared to benefit the most from hormone use.[40]

Despite the large quantity of epidemiologic and basic scientific data supporting hormone replacement therapy, there rightfully remains concern about the limitations of the studies to date. It is impossible to correct for all the potential biases in analyzing the mostly observational data. In these studies, the decision to use hormone replacement therapy was likely a personal decision of the women and their physicians. Selection bias may plausibly account for the better outcomes in women who use hormone replacement because they are more educated, see their doctors more regularly, have greater access to health care, have higher incomes, and have fewer risk factors for cardiovascular disease because they choose to lead healthier lifestyles.[41,42] These differences likely account for a large proportion of the 50% reduction in cardiovascular end points seen in studies of hormone replacement therapy.

The recently published HERS study[43] is the first prospective randomized trial of hormone replacement therapy (HRT) as secondary prevention of coronary artery disease in postmenopausal women. Interestingly, it was notably negative with respect to benefit. In this study, 2,763 women who were <80 years-old, with an intact uterus, were randomized to receive either 0.025 mg of conjugated equine estrogen plus 25 mg of medroxyprogesterone acetate, or placebo. Follow-up averaged 4.1 years. 75% of the women randomized to HRT were still taking it at the end of three years. Primary outcomes of nonfatal myocardial infarction and coronary death were not different in both groups. In fact, there was a significant trend with greater coronary heart disease events in the HRT group at one year, but less at years 4 and 5. More women in the HRT group had thromboembolism (RR 2.9) and gallbladder disease. There were no dif-

Table 2: Estrogen/progestin replacement studies and coronary artery disease.

Author	Relative risk	N	Design	End point	Significant?
Nachtigall[34] (1979)	0.33	168	clinical trial	MI	No
Hunt[35] (1990)	0.37	4544	cohort	CV death	Yes
Thompson[36] (1989)	1.36	603	case-control	stroke/MI	Yes
Falkeborn[37] (1992)	0.81	23,174	cohort	first MI	Yes
Psaty[38] (1994)	0.68	502	case-control	MI	No
Grodstein[39] (1996)	0.39	59,337	cohort	cardiovascular disease	Yes
Grodstein[40] (1997)	0.63	59,337	cohort	all-cause mortality	Yes

ferences in other secondary endpoints such as fracture, total mortality, cancer, and stroke.

The lack of benefit in this well-performed study is more than notable, in fact, it is striking. Why are the results so contrary to those of the epidemiologic studies? First, the long-discussed selection bias of women who take HRT may simply be the dominant reason why women who take HRT fare better in observational studies. The HERS may help to put into perspective the limitations and shortcomings of observational studies, and underscores just how important prospective trials are for determining clinical practice. Secondly, the addition of progestin may have offset the benefit of estrogen as several animal studies have suggested. It may be that progestins, or some forms of progestin, do "oppose" the beneficial effects of estrogen. Therefore, it will be important to test the benefits of unopposed estrogens in women with hysterectomy as this may be the only group that can benefit from estrogen therapy.

Potential risks of HRT

Despite the observed benefits on cardiovascular risk and prevention of osteoporosis, estrogen replacement therapy is clearly not without risk. The incidence of deep venous thrombosis and pulmonary embolism appear to be increased, with an observed two-fold increase among current postmenopausal estrogen users in the Nurses' Health Study.[44] A similar increase in risk was seen in the HERS. The risk of endometrial cancer is increased six-fold, an effect eliminated by addition of progestins for the woman with an intact uterus. There remains controversy over whether estrogen replacement increases the risk of breast cancer. Studies have revealed conflicting results, including meta-analyses showing either an increased risk or no effect. The Nurses' Health Study found that women using hormone therapy for greater than 10 years had an adjusted relative risk of 1.46 (95% CI, 1.20–1.76), the addition of progestins having no effect on this risk.[45] Thus, the evidence that estrogen use increases the risk of breast cancer, though compelling, is inconclusive. Once again, we lack randomized-controlled clinical trials on which to base a definitive conclusion.

Future directions

Another important large randomized, placebo-controlled study is the NIH-sponsored Women's Health Initiative. This large clinical trial aims to examine the effects of a low-fat diet, calcium supplements, and HRT on major causes of morbidity and mortality in postmenopausal women—specifically heart disease, osteoporosis, and breast and colon cancer. In the HRT arm 27,500 women will be randomized to receive estrogen replacement therapy (if having previous hysterectomy), combined estrogen/progestin replacement therapy, or placebo. Primary endpoints are mortality and morbidity from CAD. This primary prevention trial has a 9-year follow-up planned, with scheduled completion by the year 2005.

There is emerging data on selective estrogen receptor modulators. These "designer" estrogens have beneficial effects on the cardiovascular system and on bone without the untoward effects on breast and endometrial tissue. Clinical trials are under way to assess their clinical efficacy and safety.

Overall, the evidence to date from animal and human observational studies does not prove that hormone replacement therapy is effective in the prevention of CAD. The practice of cardiovascular medicine in the past two decades has been evidence-based and determined by large prospective randomized clinical trials. The HERS Study has told us more than all of the observational studies. Other prospective trials are awaited, but for now, the clinical benefit of the estrogen hypothesis remains unlikely.

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Dallas, Texas
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Abstracts of Interest

Sex hormone and atherosclerotic risk factor profiles are not determinants of coronary microvascular reserve in women with chest pain: Pilot phase results from WISE

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Background: Women with chest pain in the absence of coronary atherosclerosis (CAD) may have abnormal microvascular function with low coronary flow reserve (CFR). We assessed whether sex hormones and risk factors influence CFR in this population.

Methods: Women (n=62) in the NIH Women's Ischemia Syndrome Evaluation (WISE) with chest pain in the absence of CAD underwent assessment of coronary flow velocity response to intracoronary adenosine (18 mcg) to measure CFR. CFR was correlated with sex hormones and risk factors. These factors were also compared between those with abnormal (CFR <2.2, n=28) and normal microvascular reserve (CFR ≥22, n=34).

Results: Age correlated negatively with CFR (Spearman correlation -0.30, p=0.02). Traditional risk factors, menopause, and levels of progesterone, estrone, estradiol and lipids were not determinants of CFR. Women with abnormal microvascular reserve were older (57 vs 51 years, p=02), but had similar hormone and risk profiles compared to those with normal microvascular reserve.

Conclusion: Age is the only significant determinant of CFR in women with chest pain in the absence of CAD. Microvascular reserve abnormalities were not found to be related to menopausal status, lipids, and sex hormones.

Comparative effect of continuous combined hormone replacement therapy regimens on brachial artery blood flow

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Estrogen replacement therapy in postmenopausal women improves endothelium-dependent flow-mediated dilatation. In hormone replacement schemes progestins are required in order to reduce the likelihood of uterine malignancies. However, little is shown on the cardiovascular effect of progestins. The purpose of the study was to evaluate endothelium-dependent, flow-mediated dilatation in the brachial artery in 12 menopausal women (mean age 55±2 years) who entered a double blind, cross-over study evaluating the effect of therapy with either conjugated equine estrogens (CEE) (0.625 mg o.d.) and medroxyprogesterone acetate (MPA) (2.5 mg o.d.) or estradiol 17 ß (E2) (2 mg o.d.) and norerhisterone acetate (NETA) (1 mg o.d.) administered in a random order. Forearm vascular reactivity and blood pressure were evaluated at baseline and at the end of each period. Compared to baseline, CEE-MPA caused a mild reduction of systolic blood pressure (126 ± 12 vs 132 ± 10 mmHg) while E2-NETA increased systolic blood pressure values (138 ± 14 mmHg, p<0.01 compared to CEE-MPA). Compared to baseline, brachial artery flow-mediated dilatation was increased by CEE-MPA by 12% while it was reduced by E2-NETA by 20% (p<0.01). Brachial artery resistances were reduced by 15% by CEE-MPA while E2-NETA caused a 16% increase (p<0.01). An increase in nitroglycerine-induced brachial artery blood flow was observed after both treatment regimens, but was more pronounced after CEE-MPA (8% vs 2%; p<0.01). These data show that different estrogen-progestin treatments have different effects upon blood pressure and vascular reactivity. Compared to low-dose MPA, adding NETA to estrogens increases in peripheral vascular resistances.

Estrogen and progesterone decrease lipid loading in human female macrophages

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Background: Based on the lower incidence of atherosclerosis in females, we hypothesized that estrogen and progesterone may reduce lipid-loading in human macrophages (ie, foam cell formation).

Methods: Monocytes from healthy female donors (n=5) were plated out in phenol-red free RPMI and allowed to differentiate into macrophages over 10 days. Cells were treated from days 2-10 with either control media, 17 estradiol (2nM and 200nM) ± the estrogen receptor antagonist ICI 182 780, diethylstilbestrol (DES, non-steroidal estrogen), 17α-estradiol (17α E, inactive stereolsomer) or progesterone 10 nM. Lipid-loading was assessed by HPLC after a 48 hour incubation (days 8-10) with acetylated LDL in lipoprotein-deficient human serum. Triplicate wells were used for each condition, in each experiment.

Results: Macrophages treated with 17ß-estradiol showed a significant dose-related reduction in cholesterol ester formation vs controls (88±12% and 78±14% for 2nM and 200nM estradiol respectively vs 100±5%, p=0.04 by ANOVA). There was a similar trend in the levels of free and total cholesterol (p=0.06). These effects were not blocked by ICO 182 780. Progesterone alone (10 nM) was also associated with a marked reduction in cholesterol ester loading (16±5%, p<0.001). In contrast, DES and 17α-E did not reduce lipid loading. Estrogen exposure in male macrohages (n=4), showed no significant effect 99±13%).

Conclusion: 17ß-estradiol and progesterone reduce lipid loading inhuman female macrophages, consistent with an atheroprotective effect.