

Cardiovascular **disease** in **women**: The role of **hormone replacement therapy**

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Cardiovascular disease (CVD) is the number one cause of death in women. Premenopausal women rarely get CVD unless they are diabetics, smokers, or have hereditary hypercoagulable states. However, after the menopause and with the loss of the protective estrogenic protection, incidence of CVD increases substantially. Epidemiological studies showed a cardiovascular benefit among hormone replacement therapy (HRT) users, but the bias in these uncontrolled studies may offset any firm conclusion on the role of HRT for CVD prevention. Randomized clinical HRT trials in primary and secondary cardiovascular prevention will be discussed including HERS I and II, WHI, WISDOM, ESPRIT, ERA, and KEEPS. Due to the lack of benefit of combined HRT in preventing CVD, emphasis is now shifting towards other options such as statins, and selective estrogen receptor modulators.



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Introduction

Cardiovascular disease (CVD) is the commonest cause of mortality among women, and claims more deaths than cancer, infections, and motor vehicle accidents combined (1). Up to two-thirds of women victims of sudden cardiac deaths were previously asymptomatic. The incidence of CVD in women increases in the postmenopausal period substantially and reaches that in men at the age of 70 years. This is mainly attributed to the loss of the estrogen protective role on the vascular endothelium, plasma lipoproteins, and coagulation cascade. Despite these cardiovascular benefits of estrogen in the menstruating woman; cigarette smoking, diabetes mellitus, and hereditary hypercoagulable states predispose premenopausal women to atherosclerotic heart disease (2,3).

Women vary in their susceptibility to sustain acute coronary events. The group at highest risk are those with established coronary artery disease, prior stroke, peripheral artery disease, and abdominal aortic aneurysm (4). Also included in this group are diabetics and chronic renal patients. The estimated 10-year absolute CHD risk for these patients is >20%. On the other hand, the intermediate risk group (estimated risk 10-20%) includes women with subclinical CHD with coronary calcification, metabolic syndrome, multiple risk factors, or markedly elevated one risk factor, e.g., very high blood pressure or serum cholesterol. Early positive data on the cardiovascular protective effect of hormone replacement therapy (HRT) came from biased population-based studies. The most reputable of which was the Nurses Health

Study (NHS) which concluded that American female nurses who used HRT had less incidence of CVD over the course of many years of follow up (5). Bias could explain most of the HRT benefits among the HRT users; because these women were more educated, more likely to undergo routine check up examinations, exercise more, and lead a healthier lifestyle compared with non-HRT users.

Hence, the answer to the question of CVD protective role of HRT had to be driven from randomized, placebo-controlled studies. Since the publication of our review article in the Jordan Medical Journal in 2001 (6), several new studies have been published and thus an update was needed in this dynamic area in clinical medicine.

Heart and Estrogen/Progestin Replacement Studies I and 2 (HERS I and II)

HERS-I was a large randomized, placebo-controlled study of combined HRT (estrogen/progestin) that contradicted in its conclusions the previous positive benefits of HRT population-based studies on the incidence of cardiovascular events in postmenopausal woman with established CVD, i.e., secondary prevention (7). The mean age of the participants was age 67 years, and they were randomized to 0.625 mg/d of diethyl estrogen (DES), with or without progestin (n=1380) or placebo (n=1383) for 4 years. At the end of the follow up period, there was no reduction in the incidence of primary end points of non-fatal myocardial infarction (MI) and cardiac death among HRT users. In fact, there was an early harm effect of HRT manifested by excess cardiac events in the first year after randomization. These results made several scientific and professional bodies recommend against initiating HRT as a secondary preventive modality for postmenopausal women who already have CVD (4,8).

No convincing explanation was forwarded for the phenomenon of "HRT early harm" observed in HERS. Potential

theories include (a) increased thrombogenicity, (b) proinflammatory action of estrogen manifested by increase in serum levels of C-reactive protein and interleukin-6, and (c) undiagnosed mutations of the coagulation cascade, such as Factor V and prothrombin variant that could have predisposed women using HRT to acute cardiac events.

It was conceived that extending HERS for longer follow up period might show a benefit from HRT by overcoming the early harm factor. HERS-II was published recently, and unfortunately did not reveal any benefit after an additional 2.8 years of extended open-label use of HRT in 2321 of the original 2763 women (9).

Other clinical and angiographic secondary prevention studies reached the same conclusions. The ESPRIT study (Estrogen in the Prevention of ReInfarction Trial) found no difference in the incidence of reinfarction or death in 1017 postmenopausal women in England and Wales who were randomized within weeks of sustaining MI to receive 17 β estradiol valerate or placebo for 2 years (10).

The WELL-HART (Women's Estrogen-progestin Lipid-Lowering Hormonal Atherosclerosis Regression Trial) failed to show significant coronary atherosclerosis regression in 226 postmenopausal women (mean age 63.5 years) with at least one coronary artery lesion when receiving 17-B estradiol (+ progestin) or placebo for 3.3 years (11). The Estrogen Replacement and Atherosclerosis (ERA) study was another angiographic study which showed no positive affect of HRT on coronary artery lesion regression in 309 postmenopausal women with CAD after 3.2 years, compared with placebo (12).

Primary prevention: WHI and WISDOM

Among women with no CVD, the use of combined HRT for primary prevention was also disappointing. The American Women's Health Initiative (WHI) was prematurely terminated after 5.2 years of the proposed study period of 8.5 years. In this study, more than 16,600 healthy postmenopausal women (mean

age 63 years, range 50-79) received conjugated equine estrogen (+MPA in those with intact uterus) or placebo (13). The primary endpoint was the composite of CVD events (nonfatal MI and cardiac death) and breast cancer. Global risks and benefits were defined as the occurrence of primary endpoints, stroke, venous thromboembolism, hip fracture, colorectal cancer, and other causes of death. The incidence of invasive breast cancer in the treatment group crossed the boundary of increased risk with haz-

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ard ratio (HR) of 1.26, HR for CVD events was 1.29, and for stroke 1.41. Moreover, incidence of venous thromboembolism and gall bladder disease was higher among HRT users.

This was the first randomized trial to show increase of breast cancer incidence with HRT with just an average of 5.2 years of follow-up.

Soon after WHI was stopped, a similar primary prevention British study, Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) was also stopped. In conclusion, the role of combined HRT in CVD primary prevention was negative. One arm of WHI, women with intact uterus on unopposed estrogen, was not stopped at that time, but in March 2004, it was terminated because of failure to show cardiovascular benefits.

Further analysis from WHI revealed that among postmenopausal women aged >65 years, HRT did not improve cognitive function when compared with placebo. There was a small increased risk of clinically meaningful cognitive decline

that occurred in the HRT group (14).

More HRT studies in progress? KEEPS Trial

Would it be more advantageous to start HRT early in the perimenopause period? Some authorities consider the mean age of the WHI women of 63 years as being too late to drive a cardiovascular benefit from HRT since estrogen may slow atherosclerosis progression in the early stage of the disease, while the endothelium is still estrogen-responsive (11). To answer this question, the Kronos Early Estrogen Study (KEEPS) trial will enroll younger (age 45 to 54 years) healthy perimenopausal women (n=900) with menopausal symptoms to receive oral conjugated equine estrogen and a placebo patch, oral placebo and a transdermal patch containing estradiol, or placebo pill and patch. Women with a uterus will receive periodic progesterone. Enrollment will start by July 2004.

Non-HRT alternatives: statins

Perhaps one of the most important drawbacks of HRT trials was not using statins hand-in-hand with HRT. Timing of HRT enthusiasm vs timing of statin mega trials could explain this fact (late 1980s vs mid 1990s, respectively), but more recent HRT trials were conducted at a time when statins were shown to have a significant all-cause and cardiac mortality reduction in men as well as in women.

Statins lower mortality and morbidity when used in primary or secondary cardiovascular prevention (15-18). This effect is mediated by improving lipid profile, endothelial dysfunction, thrombogenicity, and plaque stabilization. Women in HERS who took statins for at least 3 years had a 26% lower rate of MI and coronary death. Statin use for less than 3 years was associated with a more modest 11% risk reduction, compared to non-statin users. Statin use was also associated with a 50% relative risk of venous thromboembolism (19).

The Heart Protection Study (HPS)

showed that statin use in a wide range of men and women at high risk for CHD events was associated with lower rates of cardiovascular events, venous thromboembolic events and total mortality (18). In this study, 20000 patients with CHD or at high cardiovascular risk and baseline total cholesterol >135 mg/dl were randomized by a 2 x 2 factorial design for 5 years into 4 arms: simvastatin 40 mg/day (S40) and antioxidant placebo, S40 and antioxidant, S40 placebo and antioxidant. And double placebo. This landmark study concluded that long-term therapy with simvastatin 40 mg/day produced substantial all-cause and cardiac mortality benefits as well as reduction of thromboembolic disease. The long-term tolerability profile of simvastatin was comparable to that of placebo.

Beyond their role as cardiovascular protective agents, statins decrease the risk of incidence of new onset diabetes, macular degeneration and have beneficial role in osteoporosis. A study in 575 postmenopausal women (40-75 year) and LDL-cholesterol levels of 130-190mg/dl who are at risk of osteoporosis will receive atorvastatin 10-80 mg daily for one year to study the impact on bone mineral density of lumbar spine and hip (primary endpoint), and on serum lipids and bone biomarkers (secondary endpoints).

Recent analysis of the WHI data showed less incidence of breast cancer among statin users (2.1%) compared with 3.3% among women not on lipid lowering agents, implying a 68% reduction. Statins may affect cell growth and tumor kinetics but a definite answer on the efficacy of statins in reducing incidence of breast cancer requires large controlled trials.

Recently, a growing body of evidence revealed the basic role of inflammation in the pathogenesis, progression, and acute thrombotic complications in atherosclerosis. Higher than normal serum levels of C-reactive protein (CRP), a major inflammatory marker, is associated with increased risk in healthy individuals (20,21). The Nurses Health

Study found that the incidence of MI, stroke, coronary revascularization, and cardiac death was related, among other factors, to levels of CRP and LDL-cholesterol. The majority of events (77%) occur in women with LDL-cholesterol <160 mg/dl, and 46% in those with LDL <130 mg/dl. CRP was found to be a stronger predictor of events than LDL-cholesterol. Statins can lower the CRP levels, implicating their role in modifying the vascular inflammatory response.

Non-HRT alternatives: SERMS

Selective estrogen receptor modulators (SERMs) exert estrogenic effect on serum lipids, bone, and vascular endothelium, while exerting non-trophic effects on the breast and uterus. The effect of raloxifene, a member of the SERM family, on osteoporosis was studied in the Multiple Outcomes of Raloxifene Evaluation (MORE) study which randomized more than 7700 postmenopausal women with osteoporosis to 60 or 120 mg raloxifene daily or placebo for 3 years. Raloxifene was found to reduce risk of spine fractures. It also reduced LDL-C by 15% and total cholesterol by 8.5%, without affecting serum levels of triglycerides or HDL-C. There was no net reduction of combined cardiac and cerebral events, except in a subgroup of 1035 women at high risk for stroke where there was a 68% risk reduction of all types of stroke at 4 years. There was no excess risk in the first year of the study (23,24).

A large ongoing study, Raloxifene and The Heart (RUTH) will evaluate the impact of raloxifene on the occurrence of coronary events, among other endpoints in more than 10,000 postmenopausal women with and without CAD.

Recommendations for optimal healthy life and risk factor control in women

It is evident that a healthy life style is a crucial measure that women with and without CVD have to adhere to. It is important for the treating physician to

encourage cessation of tobacco smoking, weight reduction (body mass index 18.5-24.9 Kg/m²), and regular exercise such as 30-minute brisk walking daily or on most of the days of the week. Blood pressure should be controlled, and diabetes should also be controlled to attain an HbA_{1c} serum level of <7% (4). Diet and/or lipid-lowering agents, mainly statins should be used to attain optimal serum lipoproteins levels (mg/dl) of cholesterol (<200), triglycerides (<150), and high-density lipoprotein (HDL) cholesterol (>50). Low-density lipoprotein (LDL) cholesterol level in diabetics, women with cardiovascular disease, and with multiple high risk factors should be 100 or less (8).

Aspirin should be prescribed for high and intermediate risk women. If contraindicated or intolerated, clopidogrel can be used instead. Post myocardial infarction women should receive a beta blocker and an angiotensin converting enzyme inhibitor unless contraindicated. The latter is indicated for high risk women as well, i.e., diabetics with other risk factors, and those with cerebral, aortic, or peripheral vascular disease. Two large clinical trials (HOPE and EUROPA) showed that using ramipril and perindopril, respectively, lowers overall and cardiac mortality, as well as risk for MI, stroke, and revascularization procedures in such groups of patients (25,26).

The latest recommendations (4) advise against prescribing or renewing combined HRT for CVD prevention in postmenopausal women. Other forms of HRT (e.g., unopposed estrogen) should not be initiated or continued to prevent CVD as concluded by the WHI estrogen-only trial (27). For women without CHD who have oppressive perimenopausal symptoms, HRT is extremely effective and is an appropriate choice when used for 2-4 years, as long as they realize there is a small risk of breast cancer since this relatively short period would now approach the threshold of risk as defined by WHI.

REFERENCES

1. American Heart Association. Heart disease and stroke statistics-2003 update. Dallas, TX: American Heart Association, 2002
2. Hu FB, Sampfer MJ, Manson JE, et al. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. *N Engl J Med* 2000;343:530-7
3. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Ann Rev Public Health* 1998;19:55-72
4. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *J Am Coll Cardiol* 2004;43:900-21.
5. Stampfer MJ, Colditz GA, Willet WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: 10-year follow-up from the Nurses Health Study. *N Engl J Med* 1991;325:1801-10
6. Hammoudeh AJ. Women, cardiovascular disease and hormone replacement therapy. Review article. *Jordan Medical Journal* 2001; 35: 124-31.
7. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary artery atherosclerosis in postmenopausal women. Heart Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-13
8. NCEP Expert Panel: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497
9. Grady H, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57.
10. ESPRIT Investigators. Estrogen therapy for prevention of reinfarction in postmenopausal women: a randomized placebo controlled trial. *Lancet* 2002;360:2001-8
11. Hodis HN, Mack WJ, Azen SP et al, for the Women's Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial Research Group. Hormone therapy and the progression of coronary artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003;349:535-45
12. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:422-9
13. Manson JE, Hsia J, Johnson KC, et al, for the Women's Health Initiative investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-34
14. WHI Investigators. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. *JAMA*. 2003;289:2663-2672
15. The Long-term intervention with pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Eng J Med* 1998;339:1349-1357
16. Flaker GC, Warnica JW, Sacks FM, et al. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. *J Am Coll Cardiol* 1999;34:106-112
17. Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 1998;297:1615-1622
18. Heart protection Study Collaborative Group. MRC/BHF Heart protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:7-22
19. Herrington DM, Vittenghoff E, Lin F, et al. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2002;105:2962-7
20. Albert MA, Glynn RJ, Ridker PM. Plasma concentration of C-reactive protein and the calculated Framingham coronary heart disease risk score. *Circulation* 2003;108:161
21. Albert MA, Danielson E, Rifai N, et al, for the PRINCE investigators. Effect of statin therapy on C-reactive protein levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): A randomized trial and cohort study. *JAMA* 2001;286:64-70.
22. Brian W, Lewis K, Robert W, Safia P. Effects of raloxifene on serum lipids and coagulation factors. *JAMA* 1998;279:1445-51
23. Jordan VC, Morrow M. Raloxifene is a multifunctional medicine? *BMJ* 1999;319:331-2
24. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation study investigators. *N Engl J Med* 2000;342:145-53
25. EUROPEAN trial on reduction of cardiac events with perindopril in stable coronary Artery disease (the EUROPA) investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicenter trial. *Lancet* 2003;362:782-8
26. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2004;291:1701-1712