B. Bozkurt, M.D., Ph.D.

WHERE DO WE CURRENTLY STAND WITH ADVICE ON HORMONE REPLACEMENT THERAPY FOR WOMEN?

Biykem Bozkurt, M.D., Ph.D.

Winters Center for Heart Failure Research at Baylor College of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas

Introduction

Nearly 250,000 women die each year from cardiovascular disease, making it the leading cause of death in women. The initial clinical manifestation of coronary artery disease (CAD) in women is usually 10 years later than in men on average, with the first myocardial infarction presenting 20 years later.[1–6] At any age the prevalence of CAD is lower in women, but with advancing age, this gender differential diminishes. The fact that CAD prevalence is lower in women has led to the false presumption that women are protected from cardiovascular diseases.

Since women live 8 to 10 years longer than men, the absolute number of deaths from cardiovascular disease (CVD) exceeds that of men. Although there has been a decline in the overall number of cardiovascular deaths, the coronary incidence has been increasing in women and decreasing in men. Contrary to belief, CAD causes far more deaths in women than does cancer (Figure 1).[1, 2] Consider the statistics: approximately 1 out of 3 women will die of a cardiovascular event; more than a half-million women die of CVD each year; one woman dies of CVD almost each minute in the United States; and two-thirds of the women who die suddenly have no previously recognized symptoms.[2]

Advances in diagnosis and treatment of CVD appear to have translated into a survival benefit in men but not in women. The mortality due to CVD remains high in women, with no improvement in survival trends over time compared to men (Figure 2). This may be related to differences and delays in recognizing CVD in women or in treatment strategies, and to biological differences. Women with acute coronary syndrome often delay calling for professional help and present more frequently with atypical symptoms, such as abnormal pain locations, nausea, vomiting, fatigue, and dyspnea. Women not only present later from the onset of chest pain but are also sicker at the time of diagnosis. Furthermore, there appears to be a bias against heart disease in women — both patients and their caregivers/health care providers do not recognize or treat CVD in a timely manner in women. Compared to men, women are less likely to receive appropriate treatment for heart disease such as optimal control of blood pressure, use of aspirin, cholesterol-lowering medications, thrombolytics, or referrals for interventions such as balloon/stent or bypass surgery. Women seem to be evaluated less intensively, and referrals for cardiac catheterization are 8-fold higher in men than in women. The clinical outcomes including myocardial infarction mortality, all-cause mortality, and reinfarction rates are worse in women with CVD than in men.[2]

Many risk factors contribute to CAD in women, but menopause is one of the strongest. Risk of CAD in postmenopausal women is 40 to 50% higher than in premenopausal women, and hormone replacement therapy (HRT) increases this risk. This paper discusses the myriad risk factors for CAD in women and explores the relationship between CAD and hormone replacement therapy in postmenopausal women.

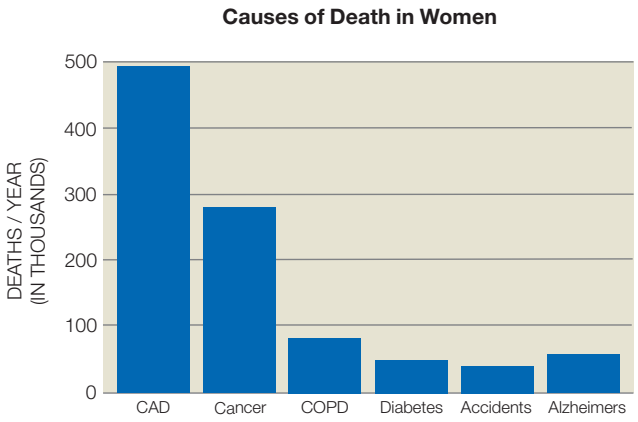
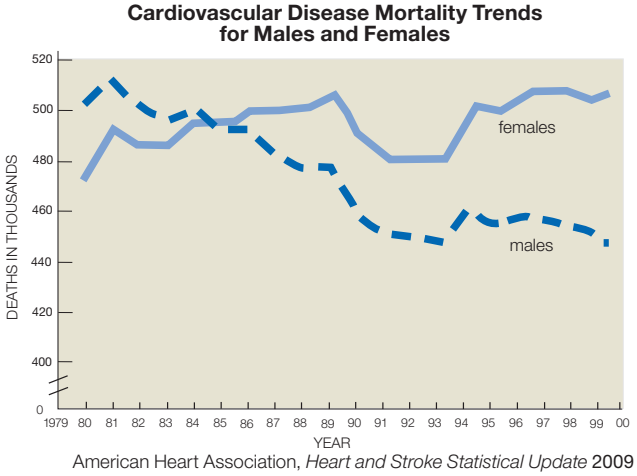


Figure 1. Causes of death in women.



American Heart Association, *Heart and Stroke Statistical Update* 2009

Figure 2. Cardiovascular mortality trends for women versus men.

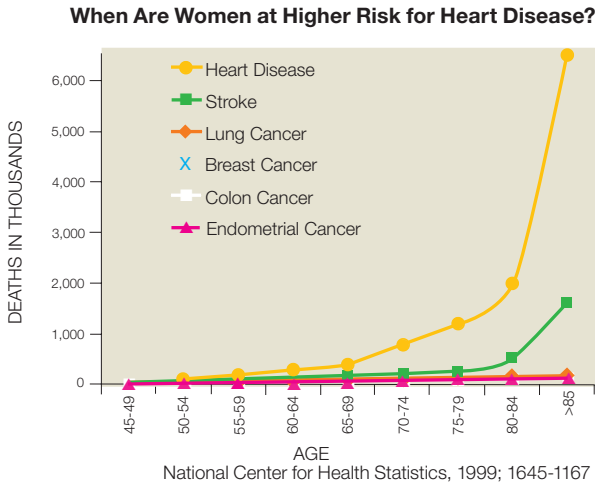
Cardiac Risk Factors Unique to Women

There are certain risk factors for CAD that are unique to women. These include postmenopausal state, HRT with estrogen and progesterone, oral contraceptives, and truncal obesity. Certain other risk factors, though common to both genders, confer higher risk for women. These include very low HDL levels (less than 45 mg/dL), high lipoprotein (a) levels, and diabetes mellitus. Low HDL is a worse risk for CAD in women. For every 10 mg/dL decline in HDL, coronary risk differs by 40–50%. The combination of high apolipoprotein B or high triglycerides and low HDL appears to be associated with a greater risk for women than for men. The mortality rate for CAD is 3- to 7-times higher among diabetic women than nondiabetic women, as compared to mortality rates being 2- to 4-times higher in diabetic men compared to their nondiabetic peers.

Other risk factors such as family history for CAD, smoking, peripheral vascular disease, hypertension, high LDL, low apolipoprotein A1 levels, and age appear to have similar cardiovascular risks for women and men. Though smoking is a similar risk for women and men, the number of beginner smokers in young women exceeds men, and the decline in women's smoking rate is less than men (6% versus 21%). Unfortunately, the average number of cigarettes women smoke have doubled since 1965, and more girls are smoking than boys. Consequently, lung cancer has surpassed breast cancer as the leading cause of cancer death among women.[7] Cardiovascular risk from oral contraceptive use is greatest in older women who smoke. Smoking has been associated with half of all coronary events in women, and the risk is elevated even in women who smoke minimally. Women are at higher risk with lifetime intake of tobacco than men. Thus, smoking appears to be a greater public health threat for women than for men.

In older age, women's overall risk associated with hypertension exceeds that of men. Hypertensive women outnumber men because of survival difference, and approximately 80% of women over age 75 will have hypertension. There is also a treatment gap with hypertension: despite recognition, hypertension does not get treated optimally in women as much as in men.[2]

The risk of CVD rises exponentially in postmenopausal women compared to premenopausal women (Figure 3). Risk of CAD in postmenopausal women is 40 to 50% higher than premenopausal women. Postmenopausal state is one of the strongest risk factors for women independent of age, equalizing the cardiovascular risk between genders. Hormone replacement therapy increases this risk. Before menopause, women have higher HDL and lower LDL levels. Following



National Center for Health Statistics, 1999; 1645-1167

Figure 3. Cause-specific mortality for different diseases, including cardiovascular disease, in women according to age.

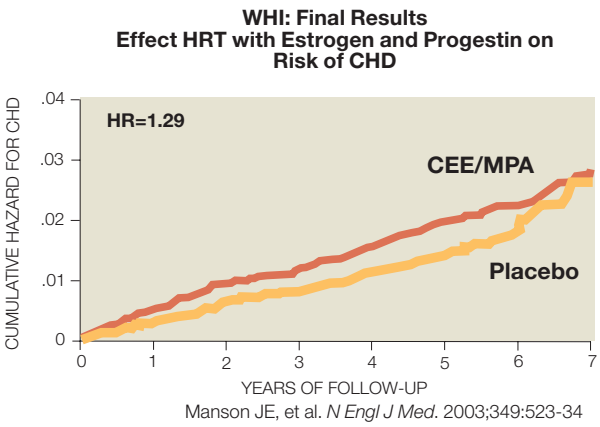


Figure 4. Effect of hormone replacement therapy on cumulative risk of cardiovascular disease in the WHI trial.

menopause, total cholesterol, LDL, and triglyceride levels rise, HDL levels remain unchanged or decrease, and the total cholesterol-to-HDL ratio increases.

Hormone Replacement Therapy in Postmenopausal Women – Primary Prevention

Historical observational studies

Prior to randomized clinical trials negating the findings of former observational studies, nonrandomized population-based trials demonstrated a 40 to 50% reduction in risk of coronary events and cardiovascular mortality in women taking estrogen. A reduction in risk in other endpoints including fatal and nonfatal myocardial infarction and sudden cardiac death, detection of coronary artery disease by coronary angiography, and success of thrombolytic therapy in the setting of acute myocardial infarction also were reported. However, most of these findings were confounded by the nonrandomized retrospective nature of the studies, with a higher representation of healthier subjects taking HRT compared to controls.[6, 8–12]

Randomized Clinical Trial (WHI)

The Women's Health Initiative Trial (WHI) was the first large-scale, randomized, multicenter study of HRT that evaluated a combination of estrogen plus progestin against placebo.[13] This study was sponsored by the National Institutes of Health. The purpose of the study was to assess long-term risks and benefits of HRT in chronic disease prevention including myocardial infarction, stroke, and cardiovascular disease. The study randomized 27,000 women aged 50–79 years (mean age 63 years) between 1993 and 1998. The study was originally scheduled to conclude in 2005 but was stopped early by the Data Safety Monitoring Board due to increased harm with HRT at 5.2 years.[14] The primary outcome was CHD events including nonfatal myocardial infarction and CHD-related death. Another primary adverse outcome was invasive breast cancer. Global risk was assessed by the effect of HRT on major disease outcomes including CHD events, breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The WHI trial showed that at the end of the trial, the risk of myocardial infarction increased by 29% (Figure 4), stroke by 41%, and venous thromboembolic events by 111%. In 10,000 women taking hormone replacement therapy, this would equate to 7 more CHD events, 8 more strokes, and 8 more pulmonary emboli.[15] Following the WHI trial, it was concluded that HRT should not be continued or started to prevent heart disease.[15]

Secondary Prevention

Historical observational studies

Again, nonrandomized population-based and angiographic trials demonstrated a greater risk reduction in women with known CAD, with the greatest benefit seen in women with the most severe disease. These findings were refuted with subsequent randomized clinical trials. The benefits of HRT found in earlier nonrandomized studies probably were due to selection bias, as women on HRT tended to lead healthier lifestyles and were more conscientious about secondary coronary risk reduction.

Randomized Clinical Trials

The first randomized large-scale trial, the Heart Estrogen-Progestin study (HERS), did not demonstrate any significant cardiovascular mortality benefit in post-menopausal women treated with estrogen and progestin over 4 years.[16] The study was conducted in 2,763 postmenopausal women with intact uteruses, all with established CAD. The mean age of the study population was 66.7 years, and follow-up was for 4.1 years. These results came as a surprise and contradicted the formerly accepted concept of a beneficial role of estrogens in cardiovascular disease.

Furthermore, during the first year, women on HRT had higher CHD mortality and nonfatal MI (4.3%) compared to placebo (2.8%). This raised safety concerns regarding initiation of estrogens for the sole purpose of reducing cardiovascular risk, which again was validated later by the WHI trial. In summary, HERS reported that in older postmenopausal women with established CAD, HRT with estrogen and progestin did not reduce overall risk for myocardial infarction and CAD death or any other cardiovascular outcome.

Of note, there was increased risk of venous thromboembolic events and gallbladder disease with estrogen treatment as reported in earlier studies. Interestingly, despite having established CAD, only 78% of the HERS population were on aspirin, 33% on beta blockers, and 45% on lipid-lowering medications, again emphasizing under-treatment of the female population with heart disease.

Possible explanations for the increased cardiovascular mortality and myocardial infarction risk in the WHI and during the first year of the HERS trial were potential increases in thrombosis, inflammation, arrhythmia, and/or ischemia with hormone replacement therapy. At present there are no specific data on causes of death to explain specific mechanisms.

The current recommendation therefore is not to initiate HRT for the sole purpose of preventing additional cardiac events in women with established CAD. For women with no known CAD, the decision to initiate HRT should rely on individual assessment of potential risks versus benefits. Women should consult their doctor about other methods of CVD prevention, such as lifestyle changes and cholesterol- and blood pressure-lowering drugs.

Pathophysiological Effects of Estrogen and Progestin

Estrogen increases HDL cholesterol by 20–30% and lowers LDL cholesterol by 10–15%; it also results in modest increases in triglyceride levels. The effects of estrogen on metabolic, coagulation, fibrosis, and inflammatory biomarkers are controversial. It has been reported to be associated with lower plasma glucose and insulin levels and procoagulant factors such as fibrinogen. It also has been reported to increase prostacyclin levels, enhance vasodilation, and reduce endothelin levels.

Progestins have an unfavorable effect on the lipid profile, biomarkers of inflammation, coagulation and fibrosis, and vascular endothelium. Progestins tend to raise LDL levels and lower HDL levels. However, the addition of progestin will significantly reduce the risk of endometrial uterine cancer, almost eliminating the excess risk of endometrial cancer due to the unopposed effect of estrogen.[17, 18]

Though there are various types of different estrogen (estrogen receptor modulators, plant or soy driven estrogens, transdermal estrogen preparations) and/or progestin preparations with different effects on lipid profile, coagulation, and glucose metabolism — and all are advocated to have a safer profile than the conjugated equine estrogen and medroxyprogesterone tested in clinical trials — these preparations have not been tested in randomized clinical trials and need to be examined in studies with clinical endpoints such as cardiovascular mortality before one is conferred to be superior than the other. Surrogate endpoints such as effects on lipid profile, coagulation, or metabolism may not be enough to declare efficacy or safety in cardiovascular disease or survival profiles.

Current Guidelines for Hormone Replacement Therapy Regarding Cardiovascular Risk

Postmenopausal women first should be screened for contraindications to hormonal therapy such as stroke, venous thromboembolism, and CAD. Then, decisions can be made individually according to the available data on each of the scenarios as listed below.

1. Postmenopausal women with no known heart disease (primary prevention):
   - Combined HRT should not be initiated for prevention of CVD in postmenopausal women (Class III, Level A).[2]
   - Combined HRT should not be initiated for prevention of CVD in postmenopausal women and should not be continued for prevention of CVD in postmenopausal women (Class III, Level A).[2, 15]
2. Postmenopausal women with known heart disease (secondary prevention):
   - Combined estrogen plus progestin hormone therapy should not be initiated to prevent CVD in postmenopausal women (Class III, Level A).[2]
   - Combined estrogen plus progestin hormone therapy should not be continued to prevent CVD in postmenopausal women (Class III, Level C).[2]
   - Other forms of menopausal HRT (e.g., unopposed estrogen) should not be initiated or continued to prevent CVD in postmenopausal women pending the results of ongoing trials (Class III, Level C).[2]

References

1. Mosca L, Manson JE, Sutherland SE, Langer RD, Manolio T, Barrett-Connor E. Cardiovascular Disease in Women: a statement for healthcare professionals from the American Heart Association. Writing Group. Circulation.1997 Oct 7;96(7):2468-82.
2. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, Grady D, Haan CK, Hayes SN, Judelson DR, Keenan NL, McBride P, Oparil S, Ouyang P, Oz MC, Mendelsohn ME, Pasternak RC, Pinn VW, Robertson RM, Schenck-Gustafsson K, Sila CA, Smith SC Jr, Sopko G, Taylor AL, Walsh BW, Wenger NK, Williams CL; American Heart Association. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation. 2004 Feb 10;109(5):672-93. Epub 2004 Feb 4.
3. Eaker ED, Chesebro JH, Sacks FM, Wenger NK, Whisnant JP, Winston M. Cardiovascular disease in women. Circulation.1993 Oct;88(4 Pt 1):1999-2009.
4. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, Speizer FE, Hennekens CH. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med. 1996 Aug 15;335(7):453-61.
5. Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, Rosner B, Fuchs C, Hankinson SE, Hunter DJ, Hennekens CH, Speizer FE. Postmenopausal hormone therapy and mortality. N Engl J Med. 1997 Jun 19;336(25):1769-75.
6. Rich-Edwards JW, Manson JE, Hennekens CH, Buring JE. The primary prevention of coronary heart disease in women. N Engl J Med. 1995 Jun 29;332(26):1758-66.
7. Silverberg E, Lubera J. Cancer statistics. CA Cancer J Clin. 1987 Jan-Feb;37(1):2-19.
8. Sidney S, Petitti DB, Quesenberry CP Jr. Myocardial Infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. Ann Intern Med. 1997 Oct 1;127(7):501-8.
9. Psaty BM, Heckbert SR, Atkins D, Siscovick DS, Koepsell TD, Wahl PW, Longstreth WT Jr, Weiss NS, Wagner EH, Prentice R, Furberg CD. A review of the association of estrogens and progestins with cardiovascular disease in postmenopausal women. Arch Intern Med. 1993 Jun 28;153(12):1421-7.
10. Koh KK, Mincemoyer R, Bui MN, Csako G, Pucino F, Guetta V, Waclawiw M, Cannon RO 3rd. Effects of hormone-replacement therapy on fibrinolysis in postmenopausal women. N Engl J Med. 1997 Mar 6;336(10):683-90.
11. Kuhn FE, Rackley CE. Coronary artery disease in women. Risk factors, evaluation, treatment, and prevention. Arch Intern Med. 1993 Dec 13;153(23):2626-36.
12. Guetta V, Cannon RO 3rd. Cardiovascular effects of estrogen and lipid-lowering therapies in postmenopausal women. Circulation. 1996 May 15;93(10):1928-37.
13. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998 Feb;19(1):61-109.
14. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.
15. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M; Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003 Aug 7;349(6):523-34.
16. Heart Estrogen-Progestin (HERS) study, preliminary results, AHA 1998.
[Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998 Aug 19;280(7):605-13.]
[Mosca L, Collins P, Herrington DM, Mendelsohn ME, Pasternak RC, Robertson RM, Schenck-Gustafsson K, Smith SC Jr, Taubert KA, Wenger NK. Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 2001; 104: 499–503.]
17. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA.1995 Jan 18;273(3):199-208.
18. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA. 1991 Apr 10;265(14):1861-7.