
HRT and Cardioprotection: Past, Present and Future

Robert Kreisberg, MD

The debate over the potential cardioprotective effects of hormone replacement therapy (HRT) has taken center stage in recent months. Several large trials have been conducted, but all are subject to specific criticisms. Most recently, the Women's Health Initiative strongly indicated that combined continuous conjugated equine estrogen and medroxyprogesterone acetate should not be used to protect the heart. Women who do not need the regimen for the relief of menopausal symptoms should have it tapered and stopped.

More and more attention is being paid to the cardiovascular health of women, especially as they age and enter the menopausal years. Coronary heart disease (CHD) is responsible for nearly one-third of the mortality in women, and women have higher morbidity and mortality than men following a myocardial infarction.¹⁻³

Throughout the premenopausal period, women are at much lower risk of developing coronary heart disease. Through menopause and beyond, it is suspected that the loss of estrogen allows atherosclerosis to develop to the degree that it does in men. Within 10 years of entering menopause, a woman's risk of developing CHD and related events is identical to that of a man 10 years her junior. In other words, a 60-year-old woman is as likely to have CHD as a 50-year-old man, presumably because of estrogen loss.

Laboratory studies have demonstrated that estrogen produces changes in the biology of the vessel wall, in endothelial function and in a variety of settings that would seem to support some epidemiologic observations that estrogen is beneficial to the heart. As randomized, controlled trials emerged, however, the observations were not what many expected.

The real question for clinicians is how to distinguish, after age 50, the effects of age versus the effects of estrogen deficiency on the heart. From this, a pertinent and increasingly important question emerges: Does hormone replacement therapy (HRT) offer any cardioprotection, either primary or secondary? This review examines some of the primary- and secondary-intervention trials that have been conducted and summarizes the results.

The Women's Health Initiative

The Women's Health Initiative (WHI) was the first randomized trial to directly address the effect of conjugated equine estrogen (CEE) at 0.625 mg/day plus medroxyprogesterone acetate (MPA) at 2.5 mg/day on CHD incidence and overall risks and benefits in healthy postmenopausal women with no pre-existing heart disease.⁴

In April 2000, the investigators issued a statement saying there was a higher risk of clinical events in the first two years for those on HRT than for those on placebo. Although small, the risk was present. The following year, a similar announcement warned of slightly increased risk for myocardial infarction, venous thromboembolism and stroke.

In July 2002, the National Institutes of Health announced it had stopped the trial after a mean of 5.2 years of follow-up because overall health risks exceeded benefits. Absolute risks per 10,000 person-years in the estrogen plus progestin group included seven more CHD events, eight more strokes, eight more pulmonary embolisms and eight more invasive breast cancers.⁵ Colorectal cancer and osteoporotic fractures were decreased, but continuous combined estrogen plus progestin was associated with many more adverse than beneficial effects.

Since all women enrolled in the trial had an intact uterus, the WHI does not provide us with any information regarding the effects of estrogen alone on the heart.

HERS and HERS II

The Heart and Estrogen/progestin Replacement Study (HERS) was designed to determine whether the combination of CEE and MPA alters the risk for CHD events in postmenopausal women with established coronary disease.⁶ In this trial, women were given either 0.625 mg of CEE and 2.5 mg of MPA or placebo and followed for an average of 4.1 years.

The hormone regimen did not reduce the overall rate of CHD events. There

were no significant differences between groups in any of the cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group experienced myocardial infarction or CHD death. The women in the hormone group had a net 11% lower LDL cholesterol level and 10% higher HDL cholesterol level. The investigators did not recommend HRT for secondary prevention of coronary heart disease.

One interesting—and unexpected—finding from the HERS trial was that the rate of clinical events in the first year of the study was about 50% higher in the women who were treated with hormones, compared with those who received placebo. In the second year, the event rate was about the same in both groups. From the second year to the fourth year, the clinical event rate was lower in the treated group. This gives the appearance of an early adverse effect and then a late cardioprotective benefit of hormones. The net effect for the entire study was that the investigators could not show that hormones were cardioprotective.

The other important observation from the HERS trial was that the early adverse effect of hormones was the result of something other than that which caused the late benefit. In other words, if estrogens are procoagulant—if they predispose to clot formation—one would expect to see the effect early in the treatment period. Women who survived would get the benefit of delayed changes, such as lipid improvements. An argument against an early adverse procoagulant effect of the CEE/MPA HRT regimen, however, is that raloxifene, which is procoagulant, did not increase the early risk of CHD events in women with established CHD.⁷

After an additional 2.7 years of follow-up, the investigators reported in HERS II that the late cardioprotective benefit in long-term users was not sustained even though approximately half the women continued the HRT regimen. Women in the treated group had statistically similar rates of coronary events when compared with the placebo group. This is in striking contrast to the continuing benefits ob-

served in the large statin trials after statins were stopped. The HRT regimen was associated with increased rates of venous thrombosis and biliary tract surgery, while rates for cardiovascular disease, bone fractures, cancer and mortality remained the same.⁸

One criticism of HERS involves the progestin used in the trial. While this may be a valid criticism, the regimen used in the study is the most commonly used HRT regimen in the United States. However, the Nurses' Health Study also observed a twofold increase in coronary events during the first year in women with prior CHD.⁹

Another criticism is that the women in HERS were elderly and had not been on estrogen previously. In other words, the trial was not representative of what clinicians are interested in—namely, the use of estrogen to prevent the development of CHD, not its use in women who had established coronary heart disease. In my opinion, this study had a very well-defined population. But in designing such studies, it is important that the risk of an event be high, so that it can be demonstrated over a relatively short period (3 to 5 years) that the intervention makes a difference.

The ERA Trial

The Estrogen Replacement and Atherosclerosis (ERA) trial also investigated the role of CEE and MPA in the treatment of heart disease.¹⁰ The study was designed to look at changes in coronary anatomy (via quantitative coronary angiography) rather than at clinical endpoints. A cohort of 309 women with angiographically verified coronary artery disease were randomized to one of three regimens: 0.625 mg of CEE per day, 0.625 mg of CEE/2.5 mg of MPA per day or placebo. The women were followed for approximately 3 years.

While both hormone regimens brought about significant reductions in LDL cholesterol and increases in HDL cholesterol, neither regimen slowed the progression of atherosclerosis. The rates of clinical cardiovascular events were similar in all groups. The net conclusion of

the ERA trial was that there was no evidence of substantial regression of coronary atherosclerosis. In fact, there were more clinical events in the treated groups than in the placebo groups.

The ERA study differed from similar studies in that approximately half the women in ERA had an intact uterus and half did not; hence the researchers were able to compare estrogen alone versus estrogen plus progesterone.

Other Studies

In the Women's Estrogen for Stroke Trial (WEST), hormone replacement showed no effect on prevention of stroke or transient ischemic attacks in women with established cardiovascular disease.¹¹ While this can be considered another piece of evidence, it is another example of trials dedicated to secondary, rather than primary, prevention.

The Nurses' Health Study was a large investigation that *did* involve a prospective observational study of postmenopausal hormone therapy in the primary prevention of cardiovascular disease.¹² The results showed cardioprotective effects, but the authors noted that "because of the design of the study, we probably underestimate duration of therapy and have restricted our ability to assess the impact of hormone therapy in the initial months of use." In other words, the design did not allow them to address the issue of whether hormones, even in primary prevention, increase the risk of early cardiovascular disease.

There seems to be general agreement in all of the studies, observational and randomized, that for secondary prevention of CHD, there are no compelling data indicating that estrogen is effective. With the results of the WHI trial, it now appears as if there also are no data to support the use of combined continuous CEE and MPA for the primary purpose of preventing development of coronary disease in healthy women. Although these results do not compromise the benefits of estrogen in reducing the risk of osteoporotic fracture and colorectal cancer, they suggest that women who are using

combined continuous CEE and MPA for the primary purpose of preventing CHD need careful re-evaluation to assess their needs and compare their risks and benefits.

Of interest, estrogen changes some surrogate markers—such as LDL and HDL cholesterol—in a manner that would indicate that it may be cardioprotective. At the same time, it also changes other surrogates, such as C-reactive protein, in the opposite direction, in a way that favors the development of a cardiac event.

Treating CHD in Women

If HRT is not indicated for primary or secondary CHD prevention, how should we treat menopausal women with this disease? Lipid-lowering therapy is very effective. There are a great deal of data concerning women and statins. Virtually every trial that has enrolled men and women has demonstrated that statins are cardioprotective in women in the same order of magnitude that they are in men. In the major statin trials, the net reduction in the risk of major coronary events in women was 46%.^{1,13} If the therapy is directed at the identifiable risk factors, women are as likely to benefit as men.

Recently, the same group of investigators who conducted the HERS trial re-examined cardiovascular events based on statin use.¹⁴ The results were striking: Statins reduced the rates of cardiovascular events, venous thrombosis and even mortality in women, regardless of HRT use. In women who were randomized to estrogen and progesterone and who were on a statin, the statin had the same protective effects that were seen in all the other statin trials. This study supports the use of statins in postmenopausal women with coronary heart disease.

Clearly, if a woman has undesirable LDL cholesterol levels, she should be on a statin. Lipid-lowering therapy is probably underutilized in menopausal women. Perhaps this is because of the ongoing perception that women on hormones have cardioprotection and do not need lipid-lowering therapy. Also, many women on

hormones have substantially increased HDL cholesterol, which is considered to be cardioprotective. The decision to use statins or not use them may relate to the perception that women do not have as many risk factors, but some of the poor outcomes for women with CHD may be related to differences in the type of medical care they receive. Studies also demonstrate that women are much more likely than men to have multiple risk factors for coronary heart disease.

Relief of Symptoms and Protecting the Skeleton

The decision to use hormones in postmenopausal women is predicated almost entirely on providing relief of menopausal signs and symptoms: hot flashes, excessive sweating, urogenital problems, etc. There is no doubt that HRT is the best way to treat these symptoms.

Should a woman continue to use estrogen at the end of this 3 to 5 years? If she does, she will likely continue it indefinitely for the primary purpose of protecting the skeleton from osteoporosis and fractures.

A recent study examined the effect of 0.3 mg conjugated estrogen (about half the standard dose), either alone or in combination with a progestin, on bone density.¹⁵ The results showed that the smaller estrogen dose was about as effective as the traditional larger dose. Unfortunately, this study just scratched the surface. While the smaller dose was protective of the skeleton, it was also having systemic effects. Other authors have shown that this dose reduces hot flashes and improves urogenital health.¹⁶ Therefore, we know that the smaller estrogen dose is systemically active, which means it may be as likely to increase breast cancer risk as the higher dose.

Ultimately, it is my opinion that the decision to continue estrogen plus progestogen in a combined continuous regimen should be centered around protecting the skeleton and investigating alternate therapies that do so without increasing the risk of breast cancer or cardiovascular events. Fortunately, there are

other drugs that protect the skeleton, including bisphosphonates (alendronate, etidronate and risedronate) and raloxifene. Thus, after taking HRT for 3 to 5 years, the woman who wishes to protect her skeleton has a range of options that includes drugs with potentially better benefit-to-risk ratios than estrogen.

Summary

CHD is a significant health concern for women, especially as they age. Before women enter the menopausal years, natural estrogen production seems to have a protective effect on the cardiovascular system. After menopause, however, the loss of estrogen may allow atherosclerosis to develop.

HRT is an effective method for treating the symptoms of menopause, such as hot flashes, night sweats and urogenital problems. Because of its systemic effects, and because its use in CHD prevention is unproven, HRT in the form of combined continuous CEE and MPA should not be used to protect the heart. For skeletal protection, bisphosphonates (alendronate and risedronate) and raloxifene are available and safe. However, raloxifene, like estrogen, predisposes to deep venous thrombosis.

For women with CHD, lipid-lowering therapy (i.e., statins) has been proven effective in many clinical trials. Statins also can be used with HRT for menopausal women.

The use of combined continuous CEE and MPA for primary CHD prevention is not indicated based upon the recent publication from the WHI.⁵ Women currently taking a CEE and MPA regimen who do not need it for relief of menopausal symptoms should have it tapered and stopped. However, women on HRT should not be alarmed by these findings and should discuss the matter with their physicians. Women who are taking estrogen alone may question whether it is safe. This part of the WHI trial is ongoing, but it is doubtful there will be a difference in outcome when it is completed. In fact, it is my suspicion that estrogen is the major cause of the adverse effects. ■

Robert Kreisberg, MD, is vice-president for Medical Affairs and dean of the College of Medicine at the University of South Alabama, Mobile.

References

1. Kreisberg RA, Oberman A. Lipids and atherosclerosis: Lessons learned from randomized controlled trials of lipid lowering and other relevant studies. *J Clin Endocrin Metab* 2002;87:423-37.
2. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet* 1999;353:89-92.
3. Vaccarino V, Krumholz HM, Yarzebski J, et al. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;134:173-81.
4. The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical trial and observational study. *Controlled Clin Trials* 1998;19:61-109.
5. The Writing Group for the Women's Health Initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321-33.
6. Hulley S, Grady D, Bush T, et al. 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;280:605-13.
7. Barrett-Connor E, Grady D, Sashegyi A, et al, for the MORE Investigators. Raloxifene and cardiovascular events in osteoporotic postmenopausal women. Four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;287:637-56.
8. Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. 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.
9. Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormones and recurrence of coronary events in the Nurses' Health Study. *Circulation* 1999;100(suppl 18):1871.
10. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-9.
11. Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9.
12. Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-41.
13. Welty FK. Cardiovascular disease and dyslipidemia in women. *Arch Intern Med* 2001;161:514-22.
14. Herrington DM, Vittinghoff E, Lin F, et al, for the HERS Study Group. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/progestin Replacement Study (HERS). *Circulation* 2002;105:2962-7.
15. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002;287:2668-76.
16. Utian WH, Shoupe D, Bachmann G, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;75:1065-79.

Your Chance to Be Heard: A Call for Manuscripts

Menopause Management is currently accepting manuscripts to be considered for publication in upcoming issues.

The official education publication of The North American Menopause Society, *Menopause Management* is the only controlled-circulation journal devoted exclusively to the health of midlife women.

Menopause Management is read by approximately 33,000 internists, OB/GYNs and other healthcare practitioners caring for midlife women.

Articles focus on practical information for incorporation into daily practice, and cover a wide range of topics related to women's health through menopause and beyond.

Manuscripts submitted to *Menopause Management* are reviewed by two members of the Editorial Advisory Board and Editor-in-Chief Wulf H. Utian, MD, PhD.

For more information about submitting a manuscript for publication, please contact:
Linda Zinn, Corporate Managing Editor, at 216/391-9100 • lzinn@en.com

