Menopause and the Heart

Chileshe Nkonde-Price, MD[a], Jeffrey R. Bender, MD[b,*]

KEYWORDS

• Menopause • Heart • Hormone replacement therapy • Cardiovascular risk

KEY POINTS

- HRT is not currently recommended solely to prevent future heart attacks in perimenopausal or postmenopausal women.
- For perimenopausal, recently perimenopausal, or even more than a decade postmenopausal women with life-disrupting vasomotor and urogenital symptoms, topical estrogens should be first considered, followed by hormone patches with the lowest effective estrogen dose possible.
- Treatment should be maintained for the shortest duration possible.
- For women who are a decade or the more after the menopause and are no longer troubled by symptoms, HRT should be discontinued.
- Whether HRT increases risk for the conditions already prevalent in older women, such as heart attacks, strokes and breast cancer, remains unclear, and is still under investigation.

INTRODUCTION

Cardiovascular disease (CVD), including coronary artery disease (CAD), peripheral arterial disease, cerebrovascular disease, and congestive heart failure, is the leading cause of death in US women. Premenopausal women are relatively protected against CVD, compared with age-matched men. However, this gender gap narrows at menopause, the incidence of CVD in women increasing sharply and continuing to increase with advancing age. This long-standing observation led to a belief that ovarian steroid hormones and, in particular, estrogens, are cardioprotective. Large databases of women taking hormone replacement therapy (HRT) for a variety of postmenopausal symptoms were retrospectively evaluated for CVD incidence. These analyses supported the aforementioned belief, as did a series of observational studies. However,

Disclosures: Dr Bender is a consultant for Merck; Dr Nkonda-Price: None.
The authors have nothing to disclose.
[a] Penn Heart and Vascular Center for Women's Cardiovascular Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [b] Section of Cardiovascular Medicine, Yale Cardiovascular Research Center, Raymond and Beverly Sackler Cardiovascular Laboratory, Yale University School of Medicine, 300 George Street, Room 773G, New Haven, CT 06511, USA
* Corresponding author.
E-mail address: jeffrey.bender@yale.edu

Endocrinol Metab Clin N Am 44 (2015) 559–564
http://dx.doi.org/10.1016/j.ecl.2015.05.005 **endo.theclinics.com**
0889-8529/15/$ – see front matter

those data generally have not been supported by randomized clinical trials (RCTs). The discordance is surprising also in light of the beneficial effects of estrogen on the vascular endothelium at the cellular and molecular levels and on blood vessels in animal CVD models. This conundrum has been a confusing and still controversial area in women's health. In this article, the observational studies and RCTs are reviewed, the gaps and perhaps weaknesses of these trials are described, the ongoing studies intended to fill these gaps are mentioned, and recommended approaches to hormone therapy (HT) in postmenopausal women are commented on.

OBSERVATIONAL STUDIES

Numerous large-scale observational studies, most commonly performed to assess benefits of multiyear HRT use in a variety of clinical conditions, included CVD in their assessment. From these studies, there were 2 consistent observations: (1) women lacking endogenous estrogen have a greater CVD risk than those with functioning ovaries and (2) HRT reduces CVD incidence and prevalence in postmenopausal women. The NHS (Nurses Health Study) was the largest of these studies.

Nurses Health Study

The NHS was a large, prospective cohort study investigating the relationship between HT and a variety of clinical conditions, including breast cancer, gall bladder disease, and, most notably for this review, CVD.[1] The study, beginning in 1976, surveyed all registered nurses aged 30 to 55 years in 11 states. A total of 122,000 nurses responded to questionnaires providing information on hormone use, the presence of cardiovascular risk factors, and the development of CVD. Participants were surveyed every 2 years over a 4-year follow-up period, with a high degree of continued participation (93% follow-up). Although some concern grew regarding an increased incidence of breast cancer, HT users appeared to have a significantly reduced risk of CVD. Criticism of the NHS included a potential selection bias, women choosing HT possibly being healthier with more favorable CVD risk profiles than non–hormone users.

RANDOMIZED CLINICAL TRIALS

To address the healthy women bias, and to perform studies in a prospective fashion, several RCTs were designed. These RCTs included CVD surrogate marker studies, secondary prevention trials, and primary prevention trials. The PEPI (Postmenopausal Estrogen/Progestin Intervention) trial randomized 875 women, aged 45 to 64 years, analyzing the effect of HT on low-density lipoprotein (LDL), high-density lipoprotein (HDL), and fibrinogen, among other clinical parameters (eg, bone density). In 1995, study conclusions included that HT improved CVD risk, given observed reductions in LDL, fibrinogen, and increases in HDL levels. PEPI thus was consistent with the aforementioned observational studies. RCTs addressing CVD events were then initiated. The 2 most influential have been HERS (Heart and Estrogen/Progestin Replacement Study) and WHI (Women's Health Initiative), which ran concurrently.

HERS: a Secondary Prevention Trial

HERS was a multicenter, randomized, blind, placebo-controlled secondary prevention trial.[2] Secondary prevention refers to reduction of coronary events in individuals with established CAD, defined as myocardial infarction (MI), coronary artery bypass surgery or percutaneous coronary intervention, or angiographic evidence of at least a 50% occlusion of 1 or more major coronary arteries. A total of 2763 postmenopausal

women with an intact uterus were randomized to either combined estrogen/progestin therapy or placebo. Postmenopausal was defined as age at least 55 years without natural menses for at least 5 years, or no natural menses for at least 1 year and serum follicle-stimulating hormone (FSH) levels greater than 40 IU/L, or documented bilateral oophorectomy, or reported bilateral oophorectomy with FSH level greater than 40 IU/L and estradiol level less than 92 pmol/L (25 pg/mL). The age range of participants was 44 to 79 years, with a mean of 67 years. All received a baseline clinical examination, electrocardiogram (EKG), and measurement of fasting lipid levels. Compliance was addressed by frequent clinical visits, with EKG and lipid profile analyses performed yearly. The primary outcome assessed was nonfatal MI or CAD-related death. Secondary outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, peripheral arterial disease, and all-cause mortality. Overall, there was no significant reduction in any of the primary or secondary outcomes achieved in the HRT arm. However, within this composite null effect, a statistically significant time trend was noted. There were more CAD events within the first year of HRT, and fewer events in years 4 and beyond. The absence of protection overall, and the increased CVD risk within 1 year, led to significant cardiovascular concerns regarding HRT use in postmenopausal women. Thus, HERS was the first in a wave of negative studies, triggering conclusions regarding a lack of support for HRT use in cardiovascular prevention. The time trend did cause speculation regarding differential early and late biological vascular effects of estrogen. Questions arose concerning prothrombotic early, and antiatherogenic late, effects. Adding weight to the HERS conclusions, the study had a robust trial design and enrolled women with a CVD risk profile similar to the National Health and Nutrition Examination Survey III database, encompassing a random sample of postmenopausal US women with known heart disease. Despite the potential to generalize the HERS results, the study population did not address whether HT would be cardioprotective in postmenopausal women without established CVD. It was acknowledged that primary prevention trials were needed.

WHI: a Primary Prevention Trial

The WHI was a large, National Institutes of Health–sponsored, multicenter, randomized, double-blind, placebo-controlled trial investigating strategies for preventing chronic diseases in postmenopausal women.[3] The wide range of chronic diseases included gallbladder disease, dementia, kidney stones, diabetes, colon cancer, breast cancer, osteoporotic fractures, venous thromboembolic disease, stroke, and heart disease. With regard to CVD, this was a primary prevention trial, because 27,000 healthy postmenopausal women had no evidence of CVD at the time of enrollment. The trial was intended to provide the definitive conclusion with regard to HT and cardiovascular risk. Postmenopausal was defined as the absence of vaginal bleeding for 6 months (12 months for younger women, age 50–54 years), documented oophorectomy, or previous use of postmenopausal HRT. The enrollee age range was 50-79 years, with a mean of 63 years, and an average of 12.5 years after menopause. Two arms consisted of combined (estrogen plus progestin) HRT or placebo in women with an intact uterus, and estrogen replacement therapy alone or placebo in women after hysterectomy. Assessed primary outcomes were nonfatal MI, CAD death, and the development of invasive breast cancer. A global health index, combining the incidence of all primary and secondary outcomes, was generated. The planned study duration was 8.5 years, but the combined HRT arm was terminated at 5 years because the global health index was significantly higher (worse) in the treatment group. Regarding CVD, there was an

increase (0.07%) in cardiovascular events in those taking hormone (both combined and estrogen alone regimens). Thus, it was concluded that HRT does not confer a cardiovascular risk benefit in healthy postmenopausal women and may increase risk. As with HERS, there was a time trend, with a greater number of CV events among hormone users in the first year, and fewer in years 4 and beyond. The WHI gained huge worldwide attention and led to a defined change in clinical practice, that of avoiding HRT in postmenopausal women, in the context of CVD.

Sorting Through the Conundrum

Since the 2002 publication of the WHI results, clinicians and scientists have reviewed the RCTs with a critical eye, attempting to explain the discordance between a logical hypothesis, many observational studies, and the more recent clinical trials. As noted earlier, the average WHI enrollment age was 63 years, 11 to 12 years older than the age at which HRT is commonly prescribed in clinical practice. In general, women enrolled in observational studies were newly menopausal. As these timing questions arose, WHI investigators reviewed the data, assessing CVD risk of HT by age decades (50–59, 60–69, 70–79 years). This secondary analysis was published in 2007. Those who were youngest had the lowest risk of coronary heart disease. Hazard ratios were highest for those in the oldest age group, and HT appeared protective in the youngest age group. Definitive conclusions could not be made about the latter, because the study was statistically underpowered to show cardiovascular protection in those within the menopausal transition group. There was also a WHI ancillary study published in 2007, using coronary artery calcium (CAC) scoring as a surrogate marker for atherosclerosis, in the 50-year to 59-year age group. Those in the estrogen treatment group had lower CAC scores than placebo control, suggesting a potential protective effect on plaque burden. Consistent with these trends, a meta-analysis of more than 39,000 women enrolled in 23 clinical trials concluded that HRT reduces coronary heart disease risk in women younger than 60 years, but not in older women. Thus, although the WHI trial was initially considered unfavorable with regard to HT and CVD, and the prescriptions for those specific hormones used in the WHI decreased by 66% in the year after the trial, those ancillary and secondary analyses supported the notion that timing of intervention and patient selection are critical in balancing HRT risks and benefits.

More recently, a long-term RCT, the Danish Osteoporosis Prevention Study, was completed.[4] A total of 1006 recently menopausal (as determined by medical and surgical history and FSH levels, mean age 49.7 years) healthy women were randomized to either HRT or no treatment, and followed for 12 to 16 years. Analysis included cumulative hazard ratios for mortality, heart failure, and MI. There were significantly favorable hazard ratios in the estrogen only (posthysterectomy) and estrogen plus progestin groups, supporting a cardiovascular primary prevention benefit for HRT when started in recently menopausal women.

RECENTLY COMPLETED TRIALS

Because of the very low cardiovascular event rates in women in those younger age groups mentioned earlier, and the fact that 16-year randomized HRT clinical trials are not common, further documentation of a favorable HRT treatment window will most likely be obtained with trials in which progressive CVD, rather than clinical event rates, are determined. There are 2 recent such clinical trials, KEEPS (Kronos Early Estrogen Prevention Study) and ELITE (Early Versus Late Intervention Trial with Estrogen).

The Kronos Early Estrogen Prevention Study

KEEPS was a multicenter, randomized, placebo-controlled US trial, following 720 healthy women for 4 years, assessing the presence and progression of subclinical atherosclerosis.[5] Enrollees were 42 to 58 years old, and within 36 months of their last menstrual cycle. They were randomized to 0.45 mg of conjugated equine estrogens, 0.05 mg weekly transdermal estradiol (both in combination with cyclic, oral micronized progesterone, 200 mg for 12 days each month), or placebo. Assessment included progression of carotid intimal medial thickness (CIMT) by ultrasonography, and accrual of CAC by computed tomography (CT) scan, as primary end point correlates of complex atherosclerosis, with progression. A variety of ancillary studies, evaluating intermediate cardiovascular metabolic, cognitive, and bone effects are still being analyzed. At the 4-year time point, mean CIMT and CAC scores were similar across all groups. Lipid levels improved in the HT group, as did insulin sensitivity (in the transdermal estrogen group). Thus, the profile of at least some risk factors and markers of atherosclerosis was better with HRT, although cardiovascular disease, by imaging, was not.

Early Versus Late Intervention Trial with Estrogen

ELITE is a single-center, randomized placebo-controlled US trial sponsored by the National Institute of Aging.[6] It was designed to compare the effects of estrogen on the progression of early atherosclerosis in 2 groups of healthy postmenopausal women: those within 6 years of menopause and those at least 10 years after menopause. Enrollees are receiving either 17-β estradiol (Estrace) or placebo (with vaginal progesterone or placebo, for the last 10 days of each month, if an intact uterus is present). As with KEEPS, primary analytical end points were CIMT by ultrasonography and atherosclerosis by cardiac CT. A total of 643 women were enrolled, with a treatment duration of 5 years. Although the results have not yet been published, Dr Howard Hodis, the senior investigator on this study, reported positive findings at the American Heart Association Scientific Sessions in November, 2104. These positive findings included a reduction in progression of vascular disease in the HRT groups, but only if HT was initiated within the first 6 years. This finding reinforces the timing hypothesis that has evolved since subset analysis of the WHI data and of more recent RCTs (**Table 1**).

Recommendations

CVD remains the number 1 cause of death in US postmenopausal women. Longstanding beliefs regarding cardioprotective effects of estrogen have been strongly

Table 1
Effect of HT on CVD incidence is summarized by 3 clinical study results

Science Revisited			
	CAD	Stroke	VTE
NHS	↓	Not accessed	Not accessed
HERS	↔	↔	↑
WHI	↑	↑	↑↑

A 0.07% increase in coronary events was detected in the WHI HT arm, although a trend toward protective (fewer events) was noted in the youngest (50–59 year) age group.

Abbreviations: ↑, increased incidence on HT; ↓, decreased incidence on HT; ↔, no difference; VTE, venous thromboembolic disease.

challenged. Conclusions are now drawn from a continuum of studies, including retrospective database analyses, observational studies, and primary and secondary prevention RCTs. After conclusion and even publication of some of these studies, secondary data analyses were performed, in attempts to define a favorable age of treatment initiation. There are 2 parallel relevant contexts and conclusions. The first relates to any current recommendation of postmenopausal HRT specifically for CVD prevention. Given the ongoing concerns, it is not within the current standard of cardiovascular care for postmenopausal women. However, statistically significant data in support of HRT use, within a specific age window, are accumulating. We remain speculative and cautiously optimistic, in light of those favorable statistical trends in women treated within the menopausal transition. We await the publication of complete results of recent clinical trials, designed specifically to assess benefit, within this age group and beyond, with great anticipation.

In addition to addressing the standard of care for CVD prevention, it is also critical to assess cardiovascular risk when HRT is deemed necessary to treat menopausal vasomotor and estrogen-deficient urogenital symptoms or beneficial to reduce menopausal bone loss and osteoporotic fractures. The International Menopause Society (IMS) reinforces that HRT is the most effective therapy for the aforementioned postmenopausal symptoms. However, it acknowledges that CVD risk is the principle risk concern of postmenopausal HRT use. If symptoms are lifestyle limiting, the IMS endorses HRT use when started during the menopausal transition, given the timing issues described earlier. Decision regarding initiating treatment beyond the age of 60 years, or continuing use past that age, when started earlier, must be individualized per patient, using conservative risk-benefit assessments, including all standard cardiovascular risks. If deemed necessary and within acceptable risk, the lowest hormone doses, effective to maintain quality of life, should be used.

REFERENCES

1. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. N Engl J Med 1985;313:1044–9.
2. 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.
3. Rossouw J, Anderson G. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;291:1701–12.
4. Schierbeck LL, Rejnmark L, Tfteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012;345:e6409.
5. Harman S, Black D, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women. Ann Intern Med 2014;161:249–60.
6. Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause 2015;22:391–401.