Menopause and the Heart

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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,

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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