

# Women and Heart Disease: Neglected Directions for Future Research

Elizabeth Barrett-Connor

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**Abstract** Before age 65, women have less heart disease than men. For many years, estrogen was the most popular explanation for this female advantage, and observational studies through the 1980s showed a lower risk of heart attacks in postmenopausal women taking “replacement” estrogen. But the Women’s Health Initiative (WHI), the first placebo-controlled trials of hormone therapy with the size and statistical power necessary to study clinical cardiovascular outcomes, did not confirm the hormone-healthy heart hypothesis. Now, at least 5 years later, the most unexpected WHI result may be how resilient the estrogen hypothesis has been. Where, beyond estrogen therapy, should we go from here to explain the striking sex differences in heart disease rates? A broader spectrum of research about the female cardiovascular advantage and its translation is needed.

**Keywords** Heart Disease · Estrogen · Timing Hypothesis · Sex Differences

Before age 65, women have less heart disease than men in every country in the world where data exist and heart disease rates are high enough for stable estimates [7]. This is true whether heart disease risk factor levels are high or low and whether heart disease incidence rates are high or low and despite differences in access to effective medical or surgical therapies.

The universality of this male/female difference suggests that it is not explained by stress or the Western diet,

sedentary lifestyle, or tobacco use. Instead, these differences point to some intrinsic and universal sex characteristic (biologic) and are unlikely to reflect gender (psychosocial) differences.

For many years, estrogen has been the most popular explanation for the female advantage. This thesis was initially based on castrate animal models and autopsy studies of oophorectomized women. These studies are problematic because sex differences in atherosclerosis do not occur naturally in intact animal models, and oophorectomized young women have lost not only estrogen but also testosterone and progesterone and other less studied ovarian hormones such as inhibin, plus their ability to have babies.

By the 1960s, the evidence that estrogen was cardioprotective was so compelling that a clinical trial was designed to test the benefit of treating *men* at high risk of a heart attack with estrogen. Because no one had any idea what was the optimal dose of estrogen for men, men were treated with very large doses, enough to cause gynecomastia, impotence, and venous thromboembolic disease [5]. Estrogen did not prevent heart attacks in men. This trial was stopped early [5].

During the next 20 years, many large observational studies in postmenopausal women showed a lower risk of heart attacks in women taking “replacement” estrogen. Animal and in vitro studies suggested a plethora of potential protective mechanisms, as did studies showing that estrogen treatment improved high-density lipoprotein cholesterol (the good lipoprotein with a sex difference) in women.

In the 1970s, the Food and Drug Administration refused to grant industry permission to say that postmenopausal estrogen could be used to prevent heart disease. This decision prompted the Women’s Health Initiative (WHI), the first placebo-controlled trials of hormone therapy with the size and statistical power necessary to study clinical

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E. Barrett-Connor (✉)  
Division of Epidemiology, Department of Family  
and Preventive Medicine, University of California, San Diego,  
Mail Code 0607, 9500 Gilman Drive,  
La Jolla, CA 92093-0607, USA  
e-mail: ebarrettconnor@ucsd.edu

cardiovascular outcomes. Neither of the WHI trials (estrogen plus progestin [8] or estrogen alone [1]) confirmed the hormone-healthy heart hypothesis. Conjugated equine estrogen, the most commonly used oral estrogen (plus a progestogen), was bad for women's hearts or (for estrogen alone) was neutral. Both regimens increased the risk of stroke and venous thromboembolic disease. These trials were stopped early [3].

Now, at least 5 years later, the most unexpected WHI result may be how resilient the estrogen hypothesis has been. Explanations for the trials' "failure" (to show what was expected) spawned many theories, most notably the narrow window of opportunity for hormone cardiovascular disease benefit implied by the "timing hypothesis," and spawned new estrogen studies with lower doses, and different regimens or routes of administration [4]. The results of these new trials are eagerly awaited, but none will have the size or duration needed to show a significant reduction in clinical events in relatively young women [4]. Also, because estrogens are carcinogens [6], it seems unlikely that estrogen for heart disease prevention will ever again be America's best-selling prescription product.

Although the results of the WHI were unwelcome, the trials were not a failure. WHI results spared millions of older women years of ineffective and potentially unsafe estrogen therapy. The WHI also raised women's (and their physicians') awareness of the dangers of heart disease in both sexes.

Where, beyond hormone replacement therapy, should we go from here to explain the striking sex differences in heart disease rates? Although several important questions are raised in this special issue on women and cardiovascular disease of the *Journal of Cardiovascular Translational Research*, some simple questions are not addressed here and have been largely neglected elsewhere.

One of my favorite unaddressed questions is why is the universal sex difference in cardiovascular events (unexplained by tobacco habit) restricted to the coronary arteries? Why is no similar universal sex difference observed for stroke? What is different about the female coronary arteries? Is it anatomy, such as, small women have small arteries, with different branching angles and more microvasculature, or is it physiology, such as, vasoreactivity, nitric oxide, or different remodeling [2]? Could some of these differences be necessary to meet women's unique compensatory needs during pregnancy, with its large demands on the circulation?

Or could the heart disease sex difference be explained by a specifically adapted immune system, necessary to retain an antigenically foreign fetus and complete a successful

pregnancy? Compared to men, women are more prone to several autoimmune diseases; what is this telling us about their inflammatory responses, susceptibility to inflammation, and heart attacks?

Candidate explanatory mechanisms for sex differences in heart disease should fit what we know about other sex differences; pregnancy is one obvious and biologically plausible area, but by no means the only opportunity. The supply of questions about sex differences in coronary artery disease is large. This new American Heart Association journal can offer a forum for a broader spectrum of research about the female cardiovascular advantage and its translation, possibly from bedside to bench.

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