Editorial: Hormones and the Heart: Controversies and Conundrums

One in three women will die from coronary heart disease (CHD) in the United States. This is in stark comparison to 1 in 25 women who will die from breast cancer. Because CHD is the leading cause of death in women, there has been an intense effort to understand the risk factors associated with CHD. CHD rates in women after menopause are two to three times those of women of the same age before menopause. This observation, along with epidemiological studies, suggested that estrogen might be a powerful agent to prevent CHD in women.

Until recently, emphasizing the potentially favorable protective effects of hormone therapy (HT) on cardiovascular endpoints was a routine part of medical practice. Observational studies (1–3) indicated a reduced relative risk of heart disease with HT and was bolstered by prospective studies that indicated favorable lipid profiles after administration of estrogen (4–7). These studies led us to believe that HT was cardioprotective, despite the fact that the benefits were often assessed by surrogate endpoints.

The Women’s Health Initiative (WHI) is a randomized, placebo-controlled clinical trial designed with the primary endpoint of cardiovascular disease. The trial was initiated, in part, due to the request of a label change to include cardioprotection on a currently marketed HT product. The results were unexpected and contrary to the observational studies that had been published to date.

Since that time, however, many explanations have been provided to explain the discrepancy between the observational trials, such as the Nurses’ Health Study (NHS), and the WHI (8–11). In addition to the usual differences in the design of observational and prospective studies, other factors regarding the populations of the NHS and the WHI are important to consider. Baseline characteristics were markedly different in these two studies. In the NHS, the age range at enrollment was 33–55 yr, compared with an average age of 63 yr in the WHI. Almost 50% of the subjects in the WHI were past or current smokers, compared with only about 7% of the NHS subjects. Body mass index was different in the two trials, with the WHI participants more obese (34% of them had body mass index >30 kg/m²). Even the administration of the HT was different (continuous combined vs. unopposed or sequential). Thus, to compare an observational study with a different population to a randomized placebo-controlled trial of older, more obese women is not a fair comparison.

There are several lines of evidence that support the theory that timing of initiation of estrogen therapy (ET) may influence the effects on the vascular system. Elegant studies by Clarkson and his co-workers (12–15) in primates suggest that timing is critical when using estrogen to protect the vascular tree. Primates that were oophorectomized and fed an atherogenic diet did not have any reduction in atherosclerotic plaque when ET was initiated after several years. In contrast, primates that were started on ET immediately after oophorectomy had plaque reduced by 70% despite an atherogenic diet. Estrogen inhibited the initiation, but not the progression of atherosclerotic lesions in mice (16). Thus, in animal models, early administration of estrogen prevented the development of atherosclerosis.

Finally, the type(s) and doses of hormone(s) provided may have differential effects. The administration of 17β-estradiol to women without CHD for 2 yr resulted in a significant reduction in subclinical atherosclerosis as measured by carotid artery intima-media thickness. The effects were the most profound in patients who were not treated for hyperlipidemia (17). In a large observational cohort study, the risk of myocardial infarction was assessed in women with diabetes mellitus. Lower doses were not associated with adverse cardiac events (18).

In this issue of JCEM, Akhrass et al. (19) add to the evidence that HT may be cardioprotective, if initiated before the onset of atherosclerosis. Coronary artery calcification, a marker for atherosclerosis (20, 21), was assessed by electron beam computed tomography. The average age of the women was 59 yr, and the average time since menopause was 9 yr, suggesting that most of these women probably initiated HT early. After adjusting for cardiac risk factors, women using HT were more likely to have low calcium scores. HT reduced the odds of having a coronary artery calcium score of greater than 400 by 50%.

So, with all the controversy, how does one explain the conundrum of these findings? Besides different populations taking varying doses and formulations of ET and the inherent differences in observational vs. prospective trials, emerging evidence suggests that estrogen receptor (ER) polymorphisms may provide an additional link. ERs are ligand-activated members of the nuclear hormone receptor superfamily. Two estrogen receptors, ERα and ERβ, are expressed in vascular cells, and tissues have been localized to endothelialial and vascular smooth muscle cells. Thus, either or both receptors could potentially mediate either a harmful or beneficial effect to coronary arteries. There is ample indirect evidence to implicate a role for ERα in the development of atherosclerosis. Specific ERα polymorphisms are associated with a phenotype that responds more favorably to estrogen with a larger increase in HDL cholesterol, a known cardioprotective risk factor (22). A different ERα polymorphism is associated with atherosclerosis in patients with hyperlipidemia (23). The absence of ERα in a male patient was associated with severe atherosclerosis as determined by the amount of coronary calcium (24). In an autopsy study, the

Abbreviations: CHD, Coronary heart disease; ER, estrogen receptor; ET, estrogen therapy; HT, hormone therapy; NHS, Nurses’ Health Study; WHI, Women’s Health Initiative.
length of the dinucleotide repeat of ERα was associated with the severity of CHD in men. All of these studies suggest, but do not prove, a role for ERα polymorphisms in the development of atherosclerotic heart disease. Other data implicate ERβ as a causative factor in the lack of cardioprotection by ET. Vascular expression of ERβ has been consistently observed in numerous studies (25–28). ERβ expression exceeded that of ERα in normal and atherosclerotic human coronary arteries of both premenopausal and postmenopausal women (25). ERβ expression exceeded ERα expression in cultured vascular smooth muscle cells from male and female human aorta, coronary, and iliac arteries (26). ERβ expression also exceeded ERα expression in normal carotid arteries of both rodents (28) and nonhuman primates (27).

What can we conclude from these studies? Proven therapies for cardiovascular disease such as lifestyle modification, smoking cessation, statins, aspirin, angiotensin-converting enzymes, and β-blockers need to be used judiciously in women with CHD. Many more questions have been raised that demand answers. How does the timing of initiation of HT effect coronary arteries? Is there a good surrogate endpoint for measurement of CHD? Are there specific and important questions.

with the hope that future research will reveal answers to these specific and important questions.

Acknowledgments


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