Teachable Moment

Myocardial infarction (MI) is the greatest risk for death in postmenopausal North American women. Data from over 30 observational studies have strongly suggested that estrogen is protective against heart disease. For example, the Nurse's Health Study showed that ever users and current users had 0.5 (95% CI, 0.3–0.8, \( P = .007 \)) and 0.3 (95% CI, 0.2–0.6, \( P = .001 \)) relative risks (RR), respectively, for coronary disease compared to never users of menopausal hormonal therapy (HT). However, the Women's Health Initiative (WHI), a large randomized controlled trial (RCT) aimed to address the effect of HT on CVD, breast cancer, and osteoporosis, discontinued the estrogen plus progestin arm because of lack of any demonstrable cardioprotective effect, excessive breast cancers (RR 1.26; 95% CI, 1.0–1.6), and an increased risk in the Global Index of Harm. The impact of these results was profound, with many women discontinuing their HT. However, when CEE was analyzed alone, the adverse effect on breast cancer virtually went away with a RR of 0.77 (95% CI, 0.6–1.0), but still there was a slight increased risk for all CVD (RR 1.12; 95% CI, 1.0–1.2).

In retrospect, the WHI was not designed to answer the question of whether estrogen can prevent heart attacks in newly menopausal women without heart disease. It enrolled older women (average age of 63) who were more likely to have advanced stages of atherosclerosis, supporting conclusions from the Heart and Estrogen/progestin Replacement Study (HERS) study, which suggested that HRT in women with known coronary artery disease might be at increased risk, at least in the first year of treatment.

With the passage of time since the landmark WHI study, there have been further re-analyses that suggested younger women on estrogen benefit disproportionately compared to older women. A 13-year follow-up of the WHI showed the group of women ages 50–59 at randomization who received CEEs had a 40% lower risk of MI than those who received placebo, whereas no effect was seen in women who were ages 60 or older at randomization. Furthermore, subsequent analyses from the WHI have shown the absolute risk of adverse effects (measured by the global index including stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and


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DO I REALLY NEED TO STOP TAKING ESTROGEN?

death) is much lower for younger women than for older women on HRT (12 excess cases per 10 000 women annually for ages 50–59 years compared to 38 for ages 70–79 years).8

In a smaller, more recent RCT, the Danish Osteoporosis Prevention Study,7 women were randomized to estrogen and norethisterone acetate or placebo if they had a uterus, and 2 mg oral estradiol or placebo if they did not. Over 16 years of follow-up, there was a reduction in CVD endpoints with an RR of 0.61 (95% CI, 0.4–0.9). These studies support a “critical window” hypothesis, suggesting women receive the greatest cardiovascular benefit from HRT when started immediately at the onset of menopause.

The recently published ELITE (Early versus Late Intervention Trial with Estradiol) trial was specifically designed to test this hormone-timing hypothesis.10 This RCT stratified postmenopausal women into either early postmenopausal (<6 years) or late postmenopausal (≥10 years) groups and randomized them to receive oral estradiol (with vaginal progesterone if they had a uterus) or placebo. The primary outcome was the rate of change in carotid-artery intima-media thickness (CIMT) assessed by ultrasound every 6 months. After 5 years of intervention, the rate of CIMT progression in the early-postmenopausal group was significantly lower in the estradiol group than in the placebo group (absolute difference 0.0034 mm/year, P = .008), whereas the rate of CIMT progression in the late-postmenopausal group was similar in the estradiol and placebo groups (difference 0.0012 mm/year, P = .29).

The Global Consensus Statement on Menopausal Hormone Therapy, endorsed by the American Society for Reproductive Medicine and the North American Menopause Society, states menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms associated with menopause, particularly for women less than 60 years of age or within 10 years of menopause.11 Furthermore, randomized clinical trials and observational data have provided evidence that MHT may actually decrease coronary heart disease and all-cause mortality when initiated in women less than 60 years of age and within 10 years of menopause.11

MHT should be considered as a safe option for symptomatic, healthy, early-menopausal patients, such as D.H., who should have the right to be involved in decisions about discontinuation of their HT regimens. Given the prevalence of heart disease in North America, if estrogen is a beneficial prevention tool, it deserves further research and dialogue between healthcare providers and their patients.

References