Estrogen and Cardiovascular Disease: Is Timing Everything?

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Cardiovascular disease (CVD) is the leading cause of death in both women and men, accounting for 1 in every 3 deaths in the United States.[1] Since the mid-1980s, CVD has killed more women than men each year. In 2011 alone, CVD caused approximately 10,000 more deaths in women than men.[1] CVD in women is a disease of aging, rarely occurring before the 6th decade of life.[2] It has been proposed that deprivation of ovarian hormones, specifically estrogen, in menopause is causally related to increased CVD risk in aging women.[3] Observational and randomized controlled trials showed differential effects of menopausal hormone therapy (MHT), which included estrogen, on CVD risk: observational studies almost uniformly suggested benefit, whereas randomized trials showed harm, particularly in elderly women who were many years postmenopausal period.[4,5]

Multiple hypotheses have been proposed to explain the differences between unfavorable effects of MHT in randomized studies and body of observational evidence supporting the beneficial effects of MHT. Prominent among these is the "timing hypothesis," which proposes that MHT started in the perimenopausal or early postmenopausal period is cardioprotective, whereas MHT begun late after menopause increases the risk of CVD.[6] In this review, the authors discuss observational studies and randomized controlled trials of MHT in women and examine the age-dependent effects of estrogen in animal models of acute vascular injury and the effects of estrogen on cellular (macrophage and vascular smooth muscle cell [VSMC]) responses to inflammatory stimuli *in vitro*.

STUDIES OF MENOPAUSAL HORMONES IN WOMEN

Observational Studies

A meta-analysis of 25 observational studies showed a decreased relative risk of CVD and coronary heart disease (CHD) in postmenopausal women taking MHT compared with those who had never taken hormones (relative risk [RR] = 0.70; confidence interval [CI], 0.65–0.75).[7] The largest and most frequently cited of these, the Nurses' Health Study (NHS), was a prospective observational study that enrolled 121,700 female nurses aged 30 to 55 years (Table 1).[8] The 20-year follow-up study of the 70,533 postmenopausal participants (accruing 808,825 person-years of follow-up) demonstrated significantly fewer CVD events, nonfatal myocardial infarctions (MIs) or fatal CHD in women on MHT compared with MHT never users after adjustment for age, body mass index, weight, diabetes history, hypertension, increased cholesterol, age of menopause, smoking and family history (RR = 0.61; 95% CI, 0.52–0.71).

The major limitations of the NHS and other observational studies are their nonrandomized design.[15] Observational studies are inherently unable to control for selection bias and for confounding differences between treatment groups. Although all participants in the NHS were female nurses, there may have been significant differences in unknown or unmeasured variables between the groups because of the nonrandomized design of the study. Further studies demonstrated that women who chose to use MHT were more often Caucasian, healthier, wealthier and had more access to health care than nonusers.[16–18] To control for these confounding factors, randomized placebo controlled trials were needed to determine the efficacy of MHT as a preventive strategy for CVD.

Randomized Controlled Trials

Heart and Estrogen/Progesterone Replacement Study

The Heart and Estrogen/Progesterone Replacement Study (HERS) was a randomized, blinded placebo controlled study that tested the effects of MHT in postmenopausal women with preexisting CHD (Table 1).[9] HERS randomized 2,763 women with a mean age of 67 years to MHT with 0.625 mg of conjugated equine estrogens (CEE) and 2.5 mg of medroxyprogesterone acetate (MPA) daily or placebo and followed them for a mean of 4.1 years. There was no significant difference in the primary outcome (nonfatal MI or fatal CHD) between the 2 groups at the end of the study (RR = 0.99; 95% CI, 0.80–1.22) (Figure 1). However, there was a significant time trend with an early increase in risk associated with MHT use and subsequent decreased risk in years 4 and 5 (year 1 relative hazard [RH] = 1.52; 95% CI, 1.01–2.29; years 4 and 5 RH = 0.67; 95% CI, 0.43–1.04, $P = 0.009$). The apparent benefit of long-term (4–5 years) MHT on occurrence of CVD events reported in the primary outcome article from the study was not confirmed in the extended (mean 6.8 years) unblinded follow-up report (RR = 0.97; 95% CI, 0.82–1.14).[19] HERS also showed that women in the MHT group were significantly more likely to have venous thromboembolic events and gallbladder disease than those on placebo.[9,19] After the demonstration in HERS that MHT did not reduce CVD events in postmenopausal women with established CHD, MHT was no longer recommended as a preventive treatment for CVD progression.

The negative results of the HERS trial, which conflicted with findings from the previous observational studies outlined above, could partially be explained by the recruitment of women with established CHD.[9,20] Use of the synthetic

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TABLE 1. Studies of menopausal hormones

Study	Type	Population	Type of MHT	Effect	Pros/cons
Nurses' Health Study[8]	Observational, 20 yr of follow-up	Over 121,000 female nurses, 70,533 postmenopausal women	0.625 and 0.3 mg CEE varying doses chosen by participants	Decreases in CHD with both 0.625 and 0.3 mg of CEE	Observational Nonrandomized Non-placebo controlled
Heart and Estrogen/ Progesterone Replacement Study[9]	Randomized, placebo controlled clinical trial	2,763 postmenopausal women with CHD	0.625 mg CEE + 2.5 mg MPA	No benefit of MHT	Mixture of estrogen and progestin was used Older women, average age 66.7 yr
Women's Health Initiative Estrogen + Progesterone[10]	Randomized, placebo controlled clinical trial	16,608 postmenopausal women with intact uterus	0.625 mg/d CEE and 2.5 mg/d MPA	Increased risk for CHD and invasive breast cancer	Stopped early because of adverse effects Older women, average age 63 yr
Women's Health Initiative Estrogen Alone[11]	Randomized, placebo controlled clinical trial	10,739 postmenopausal women with hysterectomy	0.625 mg/d CEE	No benefit to CHD, increased incidence of stroke	Stopped early because of adverse effects Older women, average age 63 yr
Danish Osteoporosis Prevention Study[12]	Prospective randomized study	1,006 healthy perimenopausal and early postmenopausal women aged 45–58 yr, 3–24 mo after last menses	2 mg E2	Decreased incidence of CVD outcomes and increased survival in MHT group	Young perimenopausal women Primarily Caucasian CVD not primary outcome
Kronos Early Estrogen Prevention Study[13]	Randomized, double-blind placebo controlled study	720 healthy postmenopausal women aged 42–56 yr, 6 to 36 mo from their last menses	0.45 mg/d oral CEE plus 200 mg oral progesterone 12 d monthly or 50 mg/d transdermal estrogen patch plus 200 mg oral progesterone 12 d monthly	No effect of MHT on CVD outcomes CIMT and CAC at 4 yr of follow-up. Decreased menopausal vasomotor symptoms	All healthy women, at low risk for CVD Does not support timing hypothesis No adverse effects in MHT group
Early vs. Late Intervention Trial with Estradiol[14]	2 × 2 randomized, double-blind placebo controlled study	643 early (<6 yr) or late (>10 yr) healthy postmenopausal women without CVD or diabetes	1 mg daily E2	Decreases in atherosclerosis in early MHT group, not late	90% compliance in MHT Supports timing hypothesis

CAC, coronary artery calcification; CEE, conjugated equine estrogen; CIMT, carotid intima-media thickness; E2, 17-β estradiol; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.