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Hormone Therapy and Heart Disease

ABSTRACT: Menopausal hormone therapy should not be used for the primary or secondary prevention of coronary heart disease at the present time. Evidence is insufficient to conclude that long-term estrogen therapy or hormone therapy use improves cardiovascular outcomes. Nevertheless, recent evidence suggests that women in early menopause who are in good cardiovascular health are at low risk of adverse cardiovascular outcomes and should be considered candidates for the use of estrogen therapy or conjugated equine estrogen plus a progestin for relief of menopausal symptoms. There is some evidence that lends support to the "timing hypothesis," which posits that cardiovascular benefit may be derived when estrogen therapy or hormone therapy is used close to the onset of menopause, but the relationship of duration of therapy to cardiovascular outcomes awaits further study. Clinicians should encourage heart-healthy lifestyles and other strategies to reduce cardiovascular risk in menopausal women. Because some women aged 65 years and older may continue to need systemic hormone therapy for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of hormone therapy and estrogen therapy should be individualized based on each woman's risk–benefit ratio and clinical presentation.

Controversy exists regarding whether hormone therapy (HT) has a cardioprotective effect. Clinical evidence accumulated over two decades has suggested that women who take estrogen plus progestin HT or estrogen therapy (ET) alone gain protection against coronary heart disease (CHD). These largely observational studies demonstrated superior cardiovascular health profiles among participants who used either HT or ET (1–8). However, the conclusions of these studies have been criticized for methodological reasons. Conflicting data from large prospective clinical trials, including the Women's Health Initiative (WHI) (9) and the Heart and Estrogen/progestin Replacement Study (HERS) (10, 11) cast doubt on the cardioprotective effects of HT and ET. More recent randomized, controlled clinical trials have been established in response to criticism of the methodologies in some studies and in order to more fully assess the role of HT and ET for CHD protection among menopausal women. Recent evidence of the cardioprotective effects of HT and ET, when administered to women close to the onset of menopause, has sparked debate regarding the possibility of a "timing hypothesis," meaning that women who recently experienced menopause may be more likely to benefit from HT than women who have been menopausal for 10 years or more or who are older than 60 years (12–14).

One randomized, blinded, placebo–controlled trial (the HERS trial) and one subsequent randomized, unblinded follow-up trial (the HERS II trial) examined whether conjugated equine estrogen and medroxyprogesterone acetate altered CHD risk among menopausal women with known CHD (10, 11). After 4.1 years and subsequent 2.7 years of follow-up respectively, these studies did not demonstrate an overall reduction in CHD risk in women with underlying heart disease. The women who received conjugated equine estrogen and medroxyprogesterone acetate exhibited a 52% increase in CHD events (nonfatal myocardial infarction or CHD death) in the first year in the HT group compared with the placebo group (42.5/1,000 person-years versus 28.0/1,000 person-years) (10). In 2002, the WHI published the initial results of its CHD prevention trial after 5.2 years of follow-up of predominantly healthy menopausal women (9). The study was terminated early because of

reports of adverse cardiovascular effects and a worsened global index (a summary of the balance of risks and benefits, including the two primary outcomes of CHD and invasive breast cancer, plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes). Not only did the use of HT fail to provide protection against CHD, but it also imparted a 29% increase in CHD-related events (37 versus 30 per 10,000 woman-years) that developed soon after randomization. Notably, most CHD events attributed to HT use were nonfatal myocardial infarctions, and there were no significant differences in overall CHD deaths (hazard ratio, 1.18; 95% confidence interval [CI], 0.70–1.97). Unlike prior randomized studies (11, 15), the WHI results associated HT use with a 41% increased risk of stroke, mostly nonfatal events (29 versus 21 per 10,000 woman-years) that became apparent between the first and second year of use (9). Time-trend analyses suggested that the risk of CHD began to occur immediately after the initiation of HT.

After a mean of 6.8 years of follow-up, the results of the ET arm of the WHI trial were published in advance of its designed observation period because of a lack of improvement in CHD risk (the primary outcome) and an increased rate of stroke (16). This ET trial revealed several notable differences from the initial WHI study publications, such as the possible modest decrease in CHD risk because of the cumulative effects of long-term use of estrogen alone. No differences in CHD incidence were observed among those who received ET compared with placebo.

Subsequent to the aforementioned WHI studies, the WHI investigators have published many follow-up studies. Consistent with previous reports, analysis directed at extricating the HT effect on CHD risk factors found superior lipid, insulin, and glucose profiles with HT compared with placebo (17).

Age and Effects of Hormone Therapy

The mean age of participants in the WHI trial was 63 years. It has been suggested that the results may not apply to women younger than 63 years who have recently experienced menopause, who are more likely to initiate treatment. In an attempt to delineate the effect of age on CHD risk with HT use, WHI data were stratified according to participant age and duration of menopause (18). This study found that the effects of ET or HT on CHD risk might depend, in part, on age at the start of the treatment; however, this conclusion may be related to the absence of underlying heart disease in the WHI population contrasted with the HERS population in which postmenopausal participants had CHD. In a subsequent WHI analysis that focused on women aged 50–59 years, when analyzed according to treatment type, a trend toward reduced total mortality with ET or HT use was noted in women generally within the first 10 years after menopause (18). When data were pooled by individual treatment type, total mortality decreased by 30% with ET or HT use (95% CI, 0.51–0.96). For women aged 50–59 years, statins and aspirin are not associated with a reduction in mortality.

The WHI Coronary Artery Calcium Study evaluated 1,064 women aged 50–59 years who were previously enrolled in the ET arm of the WHI (19). Because coronary atherosclerotic plaques have been associated with future CHD risk, the investigators used computed tomography heart imaging to determine the degree of coronary artery calcium burden. The study results indicated that the overall distribution of coronary artery calcification scores were lower among those who received ET compared with those who received placebo (P=.03). Furthermore, for those who adhered to the study medication regimen (80% medication adherence for 5 or more years), ET use was associated with a significant reduction in the coronary artery calcification (odds ratio, 0.64; 95% CI, 0.46–0.91; P=.01). This preliminary evidence, using surrogate outcome markers, needs confirmation of its clinical significance and correlation with clinical outcomes. Nevertheless, it suggests that ET may reduce CHD risk factors and may provide cardiovascular protection for women who recently experienced menopause.

Further data have suggested that women given ET immediately after oophorectomy have a lower prevalence of coronary artery calcium (20) compared with women who are not given ET after oophorectomy. Although this evidence is indirect, it does add further support to the timing hypothesis of the cardiovascular protection of ET.

Additional variables also may alter the cardiovascular effects of HT and ET, including the choice of progestin. Although synthetic medroxyprogesterone acetate is vasoconstrictive, natural progesterone is known to have vaso-relaxation effects (21, 22) and has been shown to have either a neutral or slightly salutary effect on blood pressure (23, 24). In contrast to most synthetic progestins, progesterone causes little or no reduction in high-density lipoprotein cholesterol levels (21) and has compared favorably in its effects on low-density lipoprotein cholesterol, low-density lipoprotein phospholipids, very low-density lipoprotein cholesterol, and very low-density lipoprotein triglycerides (25). Because oral micronized progesterone has been shown to provide endometrial protection from estrogen stimulation and to protect against endometrial hyperplasia and carcinoma (26–28), it may be used in lieu of synthetic progestins.

Despite the recent data, evidence is insufficient to conclude that long-term ET or HT use improves cardiovascular outcomes (12). Nevertheless, recent evidence suggests that women in early menopause who are in good cardiovascular health are at low risk of adverse cardiovascular outcomes and should be considered candidates for the use of ET or conjugated equine estrogen plus a progestin (medroxyprogesterone acetate or micronized progesterone) for relief of menopausal symptoms (13).

Ongoing studies, including the Kronos Early Estrogen Prevention Study, are evaluating alterations in surrogate CHD risk markers (including carotid intimal thickness and the accrual of coronary calcium deposition induced by HT) among participants who receive conjugated equine estrogen or transdermal estradiol patches combined with cyclic oral micronized progesterone. Another ongoing evaluation, the Early Versus Late Intervention Trial With Estradiol randomizes women based on the number of years since menopause (less than 6 years or 10 years or more) to receive either ET (oral estradiol-17β, 1 mg daily; women with a uterus will also use vaginal progesterone gel) or placebo (29). As in the Kronos Early Estrogen Prevention Study, the primary endpoint is change in carotid intima-media thickness. With an estimated conclusion date of July 2013, the Early Versus Late Intervention Trial With Estradiol will evaluate differences between early and late start of HT.

The American Geriatric Society recommends against the use of systemic estrogen, with or without progestins, in patients 65 years and older because of evidence of carcinogenic potential (breast and endometrium) and lack of cardioprotective effect and cognitive protection in older women (30). Because this recommendation has been included in a proposed Healthcare Effectiveness Data and Information Set measure, some Fellows have been notified by health plans with which they participate that they should not prescribe systemic estrogen for women aged 65 years and older. Additionally, some older patients report that insurers are no longer covering prescriptions for systemic estrogen. Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and ET should be individualized based on each woman's risk–benefit ratio and clinical presentation. Vaginal estrogen may be an option for women whose chief concern is vaginal atrophy. As part of the shared decision-making process, the gynecologist should help the patient to weigh the risks against the benefits of taking HT or ET. When Fellows prescribe systemic estrogen for these patients, they may wish to advise them to check with their insurers as to whether the prescription will be covered.

Conclusion

Menopausal HT should not be used for the primary or secondary prevention of CHD at the present time. Recent analyses suggest that HT does not increase CHD risk for healthy women who have recently experienced menopause. There is some evidence that lends support to the timing hypothesis, which posits that cardiovascular benefit may be derived when ET or HT is used close to the onset of menopause. The relationship of duration of therapy to cardiovascular outcomes awaits further study. Furthermore, additional studies on progesterone versus synthetic progestins are needed. Clinicians should encourage heart-healthy lifestyles and other strategies to reduce cardiovascular risk in menopausal women. Quality of life issues also may be considered when prescribing ET and HT. Use of HT and ET should be individualized based on each woman's risk–benefit ratio and clinical presentation. Some women may require extended therapy because of persistent symptoms.

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