AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

Position Statement on Hormone Replacement Therapy (HRT) and Cardiovascular Risk

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INTRODUCTION

In this document, AACE hopes to provide guidance to women in or entering menopause and their health care providers regarding the important issue of hormone replacement therapy (HRT) and cardiovascular risk.

Since the publication of the Women's Health Initiative (WHI) in 2002, women and their physicians have received conflicting information regarding the risk/benefit ratio of HRT. New data and re-analyses of previously published studies may clarify these inconsistencies and allow a more rational approach to the management of menopause, allowing better risk stratification based on age and the time from the onset of menopause.

BACKGROUND

There has been considerable controversy about the risk of heart disease in women using estrogen or estrogen/progesterone combination. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, markers of cardiovascular risk, including LDL, HDL and LP(a) were favorably influenced by estrogen (1). A reduction in clinical events seemed to support a benefit of estrogen therapy in the Nurses' Health Study (NHS), an observational cohort study of 70,533 women from 1976-1996, where the hazard ratio (HR) for cardiovascular events was 0.6 in users vs. non-users of estrogen (2).

In contrast, data from The Heart and Estrogen/progestin Replacement Study (HERS) trial demonstrated that, in the first year of HRT use in a group of older women with established cardiac disease, there was an increase in cardiovascular events in the first year with a decreased risk in year 3-5, which became equal to placebo by the third year. By 6.8 years of study, cardiovascular risk was equal in the treated group to the placebo group (3). Likewise, a group of 226 postmenopausal women (mean age, 63.5 years) who had at least one coronary-artery lesion was randomized to receive either placebo, micronized estrogen or estrogen plus MPA. After 3.3 years, there was no difference in the percent stenosis on angiography in follow-up compared with placebo (4).

In the WHI, a randomized primary-prevention trial in 16,608 postmenopausal women aged 50 to 79 comparing HRT [conjugated estrogen (CEE) 0.625 mg + medroxyprogesterone acetate (MPA) 2.5 mg] versus placebo, treatment was associated with a 1.24 HR of coronary heart disease (CHD) [nominal 95% confidence interval 1.00-1.54, CI after adjustment for sequential monitoring .97-1.60] (nonfatal myocardial infarction or death due to CHD). This treatment effect was most apparent at one year. In the group treated with estrogen alone, the CHD HR was 0.93 (CI 0.75-1.12, adjusted CI 0.72-1.15).

It has been observed that estrogen replacement therapy (ERT)/HRT is effective in inhibiting progression of early stage (fatty streak) atherosclerosis but that ERT/HRT is much less effective in inhibiting progression of more advanced (established plaque) atherosclerosis in vivo animal studies with direct examination of the coronary arteries. Results of monkey studies have led to the hypothesis that ERT/HRT may be more cardio protective in younger postmenopausal women with less coronary artery disease, and less effective in women with established coronary artery disease (5). For this reason, data from both the Nurses' Health Study and WHI have been reexamined to determine the effect of hormone therapy on cardiovascular risk when stratified by age or time from last menses.

The majority (approximately 80%) of the women in the Nurses' Health Study who used hormone therapy started treatment within 2 to 3 years of menopause onset. In contrast, women in the WHI averaged 63 years of age at baseline and initiated treatment at an average of 12 to 16 years after the onset of post menopause. This difference in age and time since menopause is associated with a major difference in the underlying stage of atherosclerosis, a powerful predictor of future CHD events and mortality.

The reevaluation of the Nurses' Health Study found that women beginning hormone therapy near menopause had a significantly reduced risk of CHD (RR = 0.66, 95% CI 0.54-0.80 for estrogen alone; RR = 0.72, 95% CI 0.56-0.92 for estrogen with progestin). In the subgroup of women demographically similar to those in the WHI, there was no significant relationship between HT and CHD among women who initiated therapy at least 10 years after menopause (RR = 0.87, 95% CI 0.69-1.10 for estrogen alone; RR = 0.90, 95% CI 0.62-1.29 for estrogen with progestin). Among women who began taking hormones at older ages, there was no relation between current use of estrogen alone and CHD (for women aged 60+ years, RR = 1.07, 95% CI 0.65-1.78), although there was a suggestion of possible reduced risk for combined HT (RR = 0.65, 95% CI 0.31-1.38) (6).

In a recent meta-analysis of 23 trials of HT that compared results in younger women (< age 60 or <10 years since menopause) versus older women, HT significantly reduced CHD events in the former but not in the latter. Odds ratios for HT and CHD were 0.68 (95% CI 0.48–0.96) for younger women and 1.03 (95% CI 0.91-1.16) for older women (7).

Most recently, the WHI data itself was re-evaluated to permit an analysis of the effects of HRT on cardiovascular disease based on age. There were 10,739 women in the estrogen alone versus placebo study and 16,608 in the estrogen plus progesterone versus placebo study. When both groups were combined, CHD events occurred in 396 of hormone-treated women versus 379 in the placebo group. When stratified by time since menopause, the hazard ratios for CHD were 0.76 in the women fewer than 10 years from the onset of menopause, 1.1 in those 10-19 years from onset of menopause, and 1.28 in those women more than 20 year from onset of menopause. The absolute excess of events was -6/104 person years, 4/104, 17/104 in the each time group respectively.

By age, the cardiovascular risk analysis revealed hazard ratios at age 50-59 of 0.93, at age 60-69 of 0.98, and at age 70-79 of 1.26. The absolute excess of events by age was -2/104 at age 50-59, -1/104 at age 60-69, and 19/104. Mortality HR was 0.7 at age 50-59, 1.05 at age 60-69, and 1.14 over age 70 (by age group). Cardiovascular risk was somewhat less (though not statistically significant in the estrogen alone versus estrogen plus progesterone groups at younger ages and similar in the older age groups). Coronary heart disease (CHD) incidents in women over 70 accounted for the increased risk observed in the first year. When incidents in this age group were excluded, there was no statistically increased risk of CHD in the CEE/MPA arm of the WHI (8).

In an ancillary sub study of the WHI trial of conjugated equine estrogens compared with placebo in women who had undergone hysterectomy, computed tomography of the heart was performed in 1,064 women aged 50-59 years at randomization, and again after 8.7 years. Calcified plaque in the coronary arteries is a marker for atheromatous-plaque burden and is predictive of future risk of cardiovascular events. The mean coronary artery calcium score after trial completion was lower among women receiving estrogen than among those receiving placebo. The multivariate odds ratios after adjustment for coronary risk factors were statistically significant, with about 25% reduction at all score levels. These findings support the hypothesis that early initiation of such therapy has a beneficial effect on preventing coronary artery disease (9).

The rationale that early intervention will provide cardiovascular benefit to women is the driving force behind the Kronos Early Estrogen Prevention Study (KEEPS). KEEPS is a multi-center, 5-year clinical trial that will evaluate the effectiveness of 0.45 mg of conjugated equine estrogens, 50 microg weekly transdermal estradiol (both in combination with cyclic oral, micronized progesterone, 200 mg for 12 days each month), and placebo in women aged 42-58 years within 36 months of final menstrual period. A total of 720 women are planned to be enrolled, with an anticipated close-out of the trial in 2010. The end points will include prevention of progression of carotid intimal medial thickness and accrual of coronary calcium.

RECOMMENDATION

While AACE eagerly awaits the outcome of the KEEPS trial, it seems clear from statistical analysis of previous large observational studies and randomized controlled clinical trials that young women in early menopause not only have no excess cardiovascular risk, but that benefit may indeed be shown in the future. With this in mind, and given the powerful effects of estrogen therapy in relieving menopausal symptoms, we believe that physicians may safely counsel women to use estrogen for the relief of menopausal symptoms. Each patient should be evaluated for the severity of her symptoms, her age, and specific risk factors that might impact on her use of hormonal therapy. Non-hormonal therapies should be offered to those women who decline hormonal therapy.

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