This statement was developed by the AACE Reproductive Medicine Committee comprising Dr. Rhoda H. Cobin, MD, MACE; Chair Steven M. Petak, MD, JD, FACE, FCLM; Board Liaison Maya B. Bledsoe, MD, FACE Walter P. Borg, MD Elena A. Christofides, MD, FACE Rebecca Fenichel, MD Walter Futterweit, MD, FACP, FACE Suzanne Futterweit, MD, FACOG, FACE Neil F. Goodman, MD, FACE Ira Andrew Katz, MD, FACE Alfred Wayne Meikle, MD, FACE John Edwin Nestler, MD, FACP, FACE Richard J. Sherins, MD, FACE Keith D. Smith, MD, FACE Richard J. Spark, MD, FACE M. Antonio Verso, MD, FACE Kathleen Louise Wye, MD, PhD, FACE

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 uncertainties 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 study, including early stage (fatty streak) atherosclerosis but that ERT/HRT is more cardio protective in younger postmenopausal women than in older age groups (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 5 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 postmenopausal bleeding. The finding that ERT/HRT 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+, RR = 1.07, 95% CI 0.65-1.78), although there was a suggestion of 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 (n=18,000) versus older women, HT significantly reduced CHD events in the former but not in the latter. Odds ratios for HT and CHD were 0.58 (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-used to permit an analysis of the effect 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 group. Among women who began hormone therapy within 5 years of menopause, the risk of CHD was lower among women receiving estrogen alone by 20% (p=0.006) (8). In an ancillary sub study of the WHI trial that will evaluate the effectiveness of hormone therapy started treatment within 2 years of menopause, the hazard ratios for CHD were 0.87, 95% CI 0.69-1.10 for estrogen alone; 1.1 in those more than 20 year from onset of menopause, and 1.28 in those women more than 20 year from onset of menopause. The absolute excess of events was 0.01/100 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 0.88, and at age 70-79 of 0.87, 95% CI 0.69-1.10 for estrogen alone; 0.87, 95% CI 0.69-1.10 for estrogen alone and progesterone; 1.10, 95% CI 0.87-1.43 for estrogen plus progesterone (9). There was no statistically significant difference between the two groups.

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