AACE Position: Women's Health Initiative

Background

The Women's Health Initiative is a randomized controlled primary prevention trial with a planned duration of 8.5 years (1). Between 1993-1998, 16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited for the combined menopausal hormone therapy arm of the study. Women with significant vasomotor symptoms were excluded. Participants were randomly assigned to receive conjugated equine estrogen (CEE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg daily in one tablet (n=8506) or placebo (n=8102). The primary outcome was coronary heart disease (CHD), defined as nonfatal myocardial infarction and CHD death, with invasive breast cancer as the primary adverse outcome. The study also examined secondary outcome events including stroke, deep vein thrombophlebitis, pulmonary embolus (DVT/PE), fractures, colon cancer, and endometrial cancer. In addition, 10,739 women, who had undergone a previous hysterectomy, have been randomized to receive either CEE 0.625mg daily or placebo. On May 31,2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board (DSMB) recommended stopping the estrogen/progestin trial arm because the predetermined stopping boundary for invasive breast cancer was exceeded, as was the global risk as compared with benefit statistic.

The CEE-only arm of the study did not meet the cut-off point for increased risk and is continuing and therefore the released WHI results are limited to the CEE/MPA only. For patients on other preparations of estrogen, other doses of CEE, other progestins, other routes of administration, and patients on estrogen alone, there is insufficient data to generalize from the CEE/MPA results.

The summary of the trial (table 1), absolute risks (table 2) and benefits (table 3) are included with this statement.

AACE Position

Policy: AACE believes that menopausal hormone therapy considerations must be individualized taking into consideration the benefits, risks and alternatives. It is essential for a woman contemplating menopausal hormone therapy to discuss these issues with her physician.

Limitations: AACE recognizes the limitations of the WHI study with respect to the particular preparation used (CEE/MPA) as well as the study population, which is older, more likely to have cardiovascular disease, and less symptomatic from estrogen deficiency than the typical woman being considered for menopausal hormone therapy.

Indications: In the absence of contraindications, menopausal hormone therapy is appropriate for women with moderate to severe vasomotor symptoms associated with estrogen deficiency, quality of life symptoms resulting from estrogen deficiency, and significant symptoms related to vaginal atrophy.

Although menopausal hormone therapy is also approved for the prevention of postmenopausal osteoporosis and has demonstrated fracture efficacy in the WHI CEE/MPA study, AACE strongly recommends consideration of alternative pharmacologic therapy options for prevention and treatment of osteoporosis in patients not electing to take menopausal hormone therapy. The use of periodic bone density assessments is recommended to determine if and when pharmacologic intervention is needed (2).

AACE supports the position that menopausal hormone therapy is <u>not</u> indicated solely for primary or secondary prevention of cardiovascular disease.

Use: The use of menopausal hormone therapy should be at the minimum dose that improves symptoms and used for only so long as symptoms remain significant when assessed intermittently off of therapy. Appropriate counseling regarding the risks and benefits is needed in all patients. The type of menopausal hormone therapy, route of administration and dose should be individualized based on the clinical assessment.

Table 1: Summary Of Hazard Ratios (HR) And Confidence Intervals (CI)

	CEE/MPA	Placebo	HR	Nominal 95% CI	Adjusted 95% CI
Total number of women	8506	8102			
Invasive breast cancer	166	124	1.26	**1.00-1.59**	**0.83-1.92**
Noninvasive breast cancer	40	33	1.13 (NS)		
CHD	164	122	1.29	**1.02-1.63**	**0.85-1.97**
CHD death	33	26	1.18	**0.70-1.90**	**0.47-2.98**
Nonfatal MI	133	96	1.32	**1.02-1.72**	**0.82-2.13**
Stroke	127	85	1.41	1.07-1.85	**0.86-2.31**
Fatal stroke	16	13	1.20	**0.58-2.50**	**0.32-4.49**
Nonfatal stroke	94	59	1.50	1.08-2.08	**0.83-2.70**
Pulmonary embolism	70	31	2.13	1.39-3.25	**0.99-4.56**
Deep venous thrombosis	115	52	2.07	1.49-2.87	1.14-3.74

Table 2: Absolute Rates
(Events per 10,000 women per year)

	Estrogen+ progestin	Placebo	Difference
Myocardial infarctions	37	30	+7
Breast cancer	38	30	+8
Strokes	29	21	+8
DVT/PE	34	16	+18

Table 3: Beneficial Outcome Events

	E/P Treatment	Placebo	Hazard Ratio (nominal CI)
Total number of women	8506	8102	
Hip fracture	44	62	0.66 (0.45-0.98)
Vertebral fracture	41	60	0.66 (0.44-0.98)
Other fractures	579	701	0.77 (0.69-0.86)
Endometrial cancer	22	25	0.83 (0.47-1.47)
Colorectal cancer	45	67	0.63 (0.43-0.92)

References:

1) Writing Group for the Women's Health Initiative Investigators. "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women". *JAMA*, 2002;288:321-333
2) AACE 2001 Medical Guidelines For Clinical Practice For The Prevention And Management Of Postmenopausal Osteoporosis. *Endocr Pract.* 2001;7(4): 293-312