



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Menopausal Combined Hormone Therapy Update

The Women's Health Initiative (WHI) trial is a striking example of how scientific evidence can improve prescribing practice.<sup>1</sup> Therapeutics Letter 30 reviewed the evidence on hormone replacement therapy in 1999. Evidence then available showed that long-term estrogen/progestin therapy to prevent cardiovascular disease for menopausal women with previous myocardial infarction would cause more harm than good.<sup>2</sup> This conclusion was based on data from the Heart and Estrogen/Progestin Replacement Study (HERS) randomized controlled trial (RCT).<sup>3</sup> In July 2002 the follow-up of the HERS trial (HERS II)<sup>4,5</sup> and the WHI<sup>1</sup> were published. These two trials strengthen the evidence against using combined hormone therapy to prevent cardiovascular disease.

### WHI/HERS II details

**Population of women:** WHI enrolled 16,608 healthy menopausal North American women with an intact uterus (mean age 63). The trial was stopped early (mean follow-up 5.2 years) because the independent data monitoring committee detected an excess of breast cancer in the estrogen/progestin group.<sup>1</sup> HERS enrolled 2,763 menopausal women with an intact uterus and history of coronary heart disease (mean age 67). In HERS II 2321 women were followed in an open label extension (total mean follow-up 6.8 years).<sup>4,5</sup>

**Intervention:** Both trials: daily tablet (0.625 mg of conjugated equine estrogens [CEE], plus 2.5 mg medroxyprogesterone acetate [MPA]); the control was an identical placebo tablet.

**Trial strengths:** Both trials: 1) Randomized large numbers of subjects, achieving, at baseline, an equal distribution of all known confounding factors in both groups,<sup>3,6</sup> 2) Enrolled a population of women representative of those typically treated with hormone therapy in North America, 3) Blinded both subjects and physicians to treatment allocation, 4) Used independent data and safety monitoring boards, 5) Used an independent committee to analyze, interpret, and publish the data.

**Trial limitations:** A substantial number of women in both studies stopped taking the active study drug (42% in WHI and 55% in year 6 in HERS II). This can lead to underestimation of treatment differences, but does not invalidate the differences demonstrated. In WHI loss of blinding occurred in 40.5% of the hormone therapy group and 6.8% of the placebo group. Decisions to



break treatment blinding were made primarily to manage persistent vaginal bleeding in the estrogen/progestin group. In HERS II the 2.7 years of additional follow-up was not blinded.

**Serious adverse outcomes:** Outcomes classified as serious adverse events (SAEs) are shown in the Table. The relative risk (RR) column shows that most of the values exceed 1.0, indicating that these SAEs occurred more often in women taking combined hormone therapy than in those taking placebo. The outcomes for which the difference is statistically significant are marked with an asterisk and the absolute risk increase or reduction is calculated.

**In the combined trial data, hormone therapy significantly increased stroke, venous thromboembolic events and breast cancer, and significantly decreased colorectal cancer.**

In WHI, a pre-defined composite index for a subset of SAEs (coronary heart disease, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture and death due to other causes) was significantly increased, RR 1.15 [1.04-1.27] absolute risk increase (ARI) 1.1%, number needed to harm (NNH) 91. Unfortunately neither trial reported total SAEs.

**Other adverse outcomes:** Total fractures were significantly reduced by hormone therapy in the WHI trial (RR 0.79 [0.71-0.87]) but not in HERS II (RR 1.04 [0.88-1.23]). Hysterectomy (only reported in WHI) was significantly increased by hormone therapy, 2.9%, compared with placebo, 2.3%, (RR 1.29 [1.07-1.56], ARI 0.6%, NNH 167). Biliary tract surgery (only reported in HERS II) was significantly increased by hormone therapy, 9.1%, compared with placebo, 6.2%, (RR 1.46 [1.12-1.90], absolute risk increase (ARI) 2.9%, NNH 34).



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(all Therapeutics Letters, Course Information)

**Breast cancer subgroup analysis:** In the WHI trial the increase in breast cancer was due mainly to an increased incidence in a subgroup of women (26% of the total), who were currently taking or had previously taken hormone therapy, when they entered the study (RR 2.21 [1.35-3.62]). The incidence of breast cancer was not different in the 74% of women with no prior hormone use at baseline (RR 1.07 [0.82-1.40]). This observation is consistent with the hypothesis that prolonged exposure to carcinogens is needed to cause cancers.

**Impact on hormone therapy prescribing:** The results of HERS II and the WHI trial, published in July 2002 appear to have had an effect on women and physicians in the United States; **U.S. sales of the combination product used in the trials, Prempro (Wyeth), dropped by 53% from May, 2002 to September, 2002.** Over the same period sales of Premarin, the CEE component fell by 22%.<sup>7</sup>

This Letter contains an assessment and synthesis of publications up to November 2002. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 45 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

**Conclusions**

**Implications for combined estrogen/progestin therapy**

- **Long-term combined hormone therapy leads to more harm than good in menopausal women whether they are healthy or have coronary artery disease.** It is not a defensible preventive strategy.<sup>8</sup>
- For severe vasomotor symptoms not controlled by other means, low dose estrogen (eg. 0.3 mg CEE for women without a uterus) or estrogen/progestin (eg. 0.3 mg CEE/ 1.25 mg MPA for women with a uterus) can be prescribed for symptomatic benefit, as shown by the Women's Hope RCT.<sup>9,10</sup>
- Symptomatic therapy should be limited to at most 1 – 2 years (see Therapeutics Letter 14).<sup>11</sup>
- Women prescribed combined hormone therapy should be alerted to the increased risk of venous thromboembolic disease, stroke and breast cancer, (see Table), and reminded periodically if longer-term therapy is contemplated.

**Implications for other menopausal hormone therapies**

- Until other hormone therapies (including estrogen alone or raloxifene) have been demonstrated to provide more good than harm in long-term RCTs, they cannot be recommended for preventive therapy without ignoring the lessons from these two landmark clinical trials.<sup>8</sup>

**Table. Serious adverse outcomes for estrogen/progestin versus placebo**

Outcome	Trial	Drug%	Placebo%	RR^ (95% CI)	ARR/ARI	NNT/NNH <sup>+</sup>
Total mortality	HERS	18.9	17.3	1.09 (0.93-1.28)		
	WHI	2.7	2.7	1.01 (0.84-1.21)		
	Combined			<b>1.05 (0.93-1.19)</b>		
Total coronary disease	HERS	21.0	21.2	0.99 (0.86-1.15)		
	WHI	1.9	1.5	1.28 (1.01-1.62)*	0.4	250
	Combined			<b>1.08 (0.95,1.22)</b>		
Total stroke	HERS	12.4	11.4	1.08 (0.89-1.33)		
	WHI	1.5	1.1	1.42 (1.08-1.87)*	0.4	250
	Combined			<b>1.20 (1.02-1.42)*</b>	<b>0.4</b>	<b>250</b>
Venous thrombo-embolism	HERS	3.6	1.7	2.05 (1.26-3.32)*	1.9	53
	WHI	1.8	0.8	2.15 (1.61-2.86)*	1.0	100
	Combined			<b>2.12 (1.66-2.71)*</b>	<b>1.0</b>	<b>100</b>
Breast cancer	HERS	3.6	2.8	1.26 (0.83-1.90)		
	WHI	2.0	1.5	1.28 (1.01-1.61)*	0.5	200
	Combined			<b>1.27 (1.04-1.56)*</b>	<b>0.5</b>	<b>200</b>
Colorectal cancer	HERS	1.5	1.9	0.81 (0.46-1.43)		
	WHI	0.5	0.8	0.64 (0.44-0.93)*	0.3	333
	Combined			<b>0.69 (0.50-0.94)*</b>	<b>0.3</b>	<b>333</b>
Total cancer	HERS	11.5	9.8	1.18 (0.95-1.47)		
	WHI	5.9	5.7	1.04 (0.92-1.18)		
	Combined			<b>1.07 (0.97-1.20)</b>		
Hip fracture	HERS	2.9	1.8	1.6 (0.98-2.63)		
	WHI	0.5	0.8	0.68 (0.46-0.99)*	0.3	333
	Combined			<b>0.94 (0.70-1.26)</b>		

^ calculated using Review Manager, Cochrane Collaboration. \* p < 0.05, + Duration was 5-7 years in the 2 trials. RR = Relative Risk. CI = Confidence Interval. ARR = Absolute Risk Reduction. NNT = Number Needed to Treat to prevent one event. ARI = Absolute Risk Increase. NNH = Number Needed to treat to cause one Harmful event.

**References**

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