

# A Perspective on the Women's Health Initiative Findings



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**O**n July 9, 2002, the National Heart, Lung, and Blood Institute of the National Institutes of Health announced premature termination of one component of the Women's Health Initiative (WHI). This component was designed to assess risks and benefits of hormone therapy (HT) combining estrogen with progestin in healthy postmenopausal women. The WHI data and safety monitoring board concluded that despite noteworthy benefits, the risks of this combined HT outweighed the benefits in this study population. The impact of the announcement was immediate and profound: These results not only contradicted the medical community's previous understanding of combined HT but also received much attention in the press. Millions of women suddenly felt compelled to reassess their decision to continue HT, and health care providers mobilized to address the flood of questions and requests for counseling that continue to this day.

As recently as 2002, overwhelming observational data and expert opinion led to the conclusion that for most women, benefits of HT far outweighed its risks. The clear benefits of HT included relief of vasomotor symptoms as well as prevention of osteoporosis and heart disease. Potential benefits of HT included improved quality of life (including, for example, improved sexual function), prevention of colon cancer, and protection from Alzheimer's disease. Consequently, the WHI results stunned the medical community, and in the months

after the July 2002 announcement, many major medical organizations scrambled to prepare responses and to revise guidelines.

We health care providers in the KP Northern California Region are fortunate: Within hours after reading the press release, the KP Women's Health Care leadership began preparing an educational response for prompt transmission to more than 90,000 female

Health Plan members aged 45 or older who were receiving HT. Today, our regional Clinical Guidelines (revised in October 2002) succinctly state: "The sole indication for hormone therapy (HT) is for the treatment of menopausal symptoms. When HT is elected for symptom relief, prescribe the lowest effective dose for the shortest possible time (1-5 years)."<sup>1,p1</sup>

## **Women's Health Initiative Results: Details to Date**

Health care practitioners must clearly understand this WHI study in detail if they are to apply its results to individual perimenopausal patients. Although absolute risk and calculated relative risk are difficult for many patients to understand, clinicians must be able to explain these risks as calculated for the treatment groups in the WHI study.

The estrogen-plus-progestin (E+P) arm of the postmenopausal HT

component of the WHI was designed to end in 2005 after a mean follow-up of 8.5 years but was stopped in May 2002 after a mean follow-up of 5.2 years.<sup>2</sup> The 16,608 women eligible for the study had an intact uterus and were randomized to treatment groups who received either a tablet containing 0.625 mg conjugated equine estrogen combined

**The study found that use of E+P was associated with increased risk of CHD, breast cancer, stroke, and pulmonary embolism ...**

with 2.5 mg medroxyprogesterone acetate (PremPro) or a placebo tablet. Primary outcomes were coronary heart disease (CHD) and breast cancer. Secondary outcomes were stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death from other causes.<sup>2</sup> Results of comparing health benefits and risks were summarized by using a global index, defined as the earliest occurrence of any study outcome (giving extra statistical weight to the seven listed diseases). Randomized participants in both groups had these baseline characteristics: mean age 63 years; race/ethnicity 84% white, 7% black, 5% Hispanic; 74% had never used HT; mean BMI 28.5; mean blood pressure 128/76 mmHg; 50% had never smoked; 90% had at least one term pregnancy; 87% had normal serum cholesterol levels; and few had clinically significant chronic medical conditions.<sup>2</sup>

At the tenth interim analysis of the

study data, the data and safety monitoring board recommended that the E+P arm of the trial be stopped because predetermined limits for increased risk of breast cancer and for the global index had been exceeded. The study found that use of E+P was associated with increased risk of CHD, breast cancer, stroke, and pulmonary embolism and with decreased risk of colorectal cancer and hip fracture. No difference in mortality was seen between groups, but overall health risks exceeded benefits for the group using E+P.<sup>2</sup>

Table 1 summarizes key study findings and may be useful for showing patients alternative perspectives on the same data. This tabular summation can facilitate patient counseling and can help us to tailor treatment to the needs of individual patients.

For example, annualized absolute risk of stroke (ie, the percentage of group participants who had a stroke

during each study year) was 0.21% for the placebo group and was 0.29% for the E+P group. Thus, the projected ten-year risk of stroke is 2.1% for the placebo group and is 2.9% for the E+P group; in contrast, the projected 10-year risk of no stroke is 97.9% for the placebo group and is 97.1% for the E+P group. An alternative perspective would compare the 21 cases of stroke expected per 10,000 person-year in the placebo group with the 29 cases expected per 10,000 person-year in the E+P group; thus, a group of 10,000 women who take E+P for one year might have eight more cases of stroke than if they took a placebo. This comparison would show a 41% increased risk of stroke in the E+P group, who would be 1.29 times more likely to have a stroke than the placebo group (RR=1.29). Asymptomatic perimenopausal women balancing the potential benefit and risk of HT might weigh “a

41% increased risk of stroke after one year of using E+P” or “1.29 times more likely to have a stroke” differently than “a 97.1% chance (risk) of not having a stroke after 10 years of using E+P.” Our challenge as clinicians is to interpret findings for

patients in an unbiased, easily understood way so that our patients can be better informed when making decisions about their health care. The WHI is more than a single study—it is a large, 15-year research program based in the United States and designed to study major causes of death, disability, and frailty in postmenopausal women. The goal of the WHI is to use prevention and intervention strategies and risk factor identification to reduce incidence of CHD, breast and colorectal cancer, and osteoporotic fracture in

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<b>Table 1. Summary of key findings of the Estrogen-Plus-Progestin component of the Women's Health Initiative Hormone Replacement Therapy Clinical Trial<sup>a2</sup></b>									
Outcome	Placebo (n = 8506)			Estrogen plus progestin (n = 8102)			Estrogen plus progestin versus placebo		
	Projected 10-year risk <sup>b</sup>		Events per 10,000 person-year	Projected 10-year risk <sup>b</sup>		Events per 10,000 person-year	Difference in event risk (%)	RR	Difference in number of events per 10,000 person-year
	Event (%)	No event (%)		Event (%)	No event (%)				
<b>Increased risk:</b>									
CHD <sup>c</sup>	3.0	97.0	30	3.7	96.3	37	+29	1.29	+7
Stroke <sup>d</sup>	2.1	97.9	21	2.9	97.1	29	+41	1.41	+8
VTE <sup>c</sup>	1.6	98.4	16	3.4	96.6	34	+211	2.11	+8
Breast cancer <sup>e</sup>	3.0	97.0	30	3.8	96.2	38	+26	1.26	+8
<b>Decreased risks:</b>									
Hip fracture <sup>d</sup>	1.5	98.5	15	1.0	99.0	10	-34	0.66	-5
Colon cancer <sup>f</sup>	1.6	98.4	16	1.0	99.0	10	-37	0.63	-6
<b>Overall risk versus benefit:</b>									
Global index (any event)	15.1	84.9	151	17	83.0	170	+15	1.15	+19

<sup>a</sup> CHD = coronary heart disease, including death from CHD and nonfatal myocardial infarct;

VTE = venous thromboembolism, including deep vein thrombosis and pulmonary embolism; RR = relative risk.

<sup>b</sup> 10-year projected event risk calculated as annualized event rate × 10.

<sup>c</sup> Results evident during first trial year.

<sup>d</sup> Results evident after first trial year.

<sup>e</sup> Results evident after fourth trial year.

<sup>f</sup> Results evident after third trial year.

women. Major components of the WHI include three clinical trials evaluating promising-but-unproven approaches to prevention; an observational study identifying predictors of disease; and a study evaluating community-based approaches to adopting healthful behavior. Results of major WHI studies on effects of E+P use on health-related quality of life,<sup>3</sup> global cognitive function,<sup>4</sup> and dementia and mild cognitive impairment were published in the first half of 2003.<sup>5</sup> We can expect many more such publications in the future. Often, more questions than answers will result from these studies; health care practitioners will need not only to critically assess the clinical significance, scope, and magnitude of study findings but also to develop tools that will enable our patients to do the same. ❖

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## The Obvious

Everything you've learned in school as 'obvious' becomes less and less obvious as you begin to study the universe. For example, there are no solids in the universe. There's not even a suggestion of a solid. There are no absolute continuums. There are no surfaces. There are no straight lines.

*R Buckminster Fuller, 1895-1983, engineer, designer, and architect*