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Review

The Women's Health Initiative trial and related studies: 10 years later: A clinician's view

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ABSTRACT

The Women's Health Initiative (WHI) assessed the long-term effects of hormone therapy (HT) in postmenopausal women. The WHI started HT treatment on women aged 50–79 years in order to ascertain these effects. The study was ended early, due to findings of increased risk of coronary heart disease, breast cancer, stroke, and thromboembolic complications in women receiving estrogen plus progestin, compared to placebo. An increased risk of thromboembolic complications was also demonstrated in the estrogen only component of the WHI. The WHI results were initially reported for all subjects, and showed little difference when data were not analyzed by age. New WHI sub-analyses stratifying results by age, and an extended follow-up of the WHI offer a more complete picture of the effects of HT, revealing that starting HT in postmenopausal women less than ten years from last menstrual period appears to have less risk. In addition, hysterectomized women treated with estrogen only in the WHI have showed less risk of adverse outcomes than women in the estrogen plus progestin group.

In this paper, we review data supporting the use of HT administered to postmenopausal women, showing it to have more benefit than risk for symptom control, prevention of bone mineral loss and fracture, and improvement of the metabolic profile in women who began HT when they were less than 60 years of age and had their last menstrual period less than ten years previous. In hysterectomized women treated with estrogen only, a reduction in breast cancer risk was noted in all age groups.

The WHI raised many important questions. Ten years later, some have been answered, including confirmation that HT for most newly menopausal women is safe and effective. The treatment of the aging woman, including hormone treatment after menopause, should remain one of our highest research priorities.

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Contents

Abbreviations: WHI, Women's Health Initiative; HT, hormone therapy; RCT, randomized clinical trial; CEE, conjugated equine estrogen; E + P, estrogen plus progesterone; ET, estrogen alone; CaD, calcium and vitamin D; VTE, venous thromboembolism; CAC, coronary artery calcium; BMI, body mass index; MRI, magnetic resonance imaging; TTP, testosterone transdermal patch.

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1. Introduction

A decade has passed since the announcement of the Women's Health Initiative (WHI) results, the publication of which led to much debate and confusion regarding the safety, efficacy, and appropriate use of hormone therapy (HT). Over this time, new data on outcomes of HT have emerged, bringing clarity to many of the issues raised by the initial WHI report. A review of this evidence-based information is provided here, to guide clinicians and patients in the decision to use or not use HT.

2. Review of the Women's Health Initiative

The Women's Health Initiative was a multi-center, double-blinded placebo-controlled primary prevention trial to assess long-term health outcomes, using a "global health index" This global health index evaluated long term health benefits such as fracture risk, heart disease and stroke over a 7–10 year period (1) in postmenopausal women receiving HT or a separate study of calcium and vitamin D supplementation. It also included a non-intervention (observation) arm, which will not be discussed in this paper. The WHI began in the 1990s and reported its main findings in 2002 and 2004. Since then, the WHI investigators have performed sub-studies to assess outcomes in multiple health areas. These were wide-ranging and include quality of life measures, central nervous system disease, and cancer occurrence. Treatment arms in the WHI included combined estrogen (conjugated equine estrogen, CEE) plus progestin (medroxyprogesterone acetate) (E + P) for women with a uterus, CEE alone for women without a uterus (ET), and dietary supplementation with calcium and vitamin D (CaD), each arm versus placebo [1].

There were notable issues regarding the choice of subjects in the WHI. Significant vasomotor symptoms were a reason for exclusion in 90% of potential subjects in both the E + P and ET arms. The subjects were between 50 and 79 years of age at registration, with the average age 63.3 years, approximately 12 years since the menopause. Women were randomized to receive HT regardless of whether they had symptoms of hormone deficiency or not. HT was given at any age, up to 79 years [1,2].

The WHI results of treatment with E + P versus placebo were most significant for the demonstration of increased absolute risk by age of venous thromboembolism, coronary events, stroke, and the diagnosis of breast cancer [3–7] (see Fig. 1). The increased risk of invasive breast cancer, as well as the failure to demonstrate an overall health benefit led to the trial being ended after only 5.8 years [3]. This was similarly seen in two other trials, in which the similar E + P regimens was used and breast cancer incidence was reported [8,9].

The WHI estrogen alone trial (ET) showed no overall protection against myocardial infarction, coronary heart disease, or overall mortality in postmenopausal women [10]. There was an increased risk of ischemic stroke in women of all age groups [11]. The risk of venous thromboembolism (VTE) was increased, particularly within the first two years of estrogen use, but the overall risk of VTE was less than that seen with combined E + P therapy [12] (see Fig. 2). For the first time, the ET group statistically confirmed a decreased risk of femoral neck fractures for patients taking estrogen [13]. There was also a lower risk of coronary heart disease in women age 50–59 years, and a decrease in breast cancer diagnosis (−23%) approaching statistical significance ($P = 0.06$) [10,11].

Additional data have been published in the years since these initial WHI reports. It has become increasingly apparent that adverse effects of hormone therapy occur with greater frequency among older women, particularly those who begin treatment 10 or more years after the age of menopause. These new data deal with timely institution of hormone therapy during the early menopause. With this review, we hope to assist clinicians and their patients in determining whether to use HT during the menopause.

3. New data emerging

Since the discontinuation of the WHI, follow up studies have assessed within-group differences and long-term health outcomes after cessation of hormone therapy. For example, ongoing benefits with respect to breast cancer risk have been seen after the use of ET. LaCroix et al. showed that women who stopped taking ET after a median of 5.9 years of treatment and were followed for a mean of 10.7 years after discontinuation of therapy had a decreased risk of breast cancer approaching statistical significance (hazard ratio, HR, 0.75, 95% CI 0.51–1.09). This follow up also showed a decreased risk of deep vein thrombosis (HR 0.63, 95% CI 0.41–0.98), no significant increase in risk of hip fracture (HR 1.27, 95% CI 0.88–1.82), and no significant difference in total mortality (HR 1.00, 95% CI 0.84–1.18) when ET was compared to placebo [14] (see Fig. 3). In addition, the authors found that a global index compiling these outcomes outcome was more favorable among younger subjects (age 50–59, HR 0.85, 95% CI 0.70–1.03; age 60–69, HR 1.0, 95% CI 0.89–1.13; age

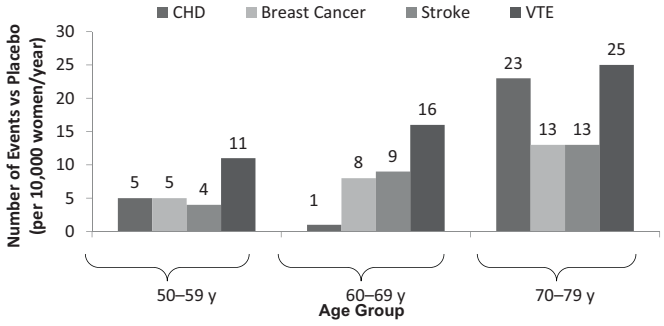

Fig. 1. WHI E + P trial: absolute risk by age.
Derived from Refs. [4–7].

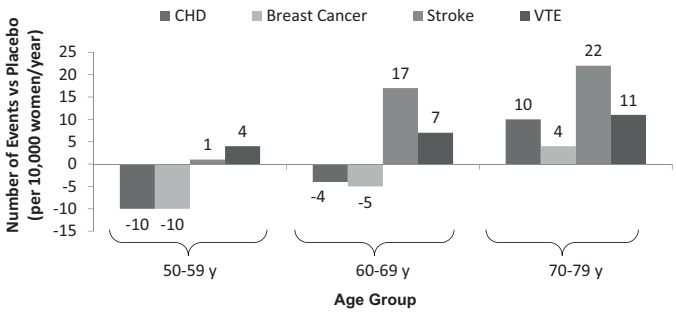

Fig. 2. WHI ET trial: absolute risk by age.
Derived from Refs. [10–13].

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