

WHI Hormone Therapy Trials Overview

Background

Prior to the WHI, previous observational studies suggested that postmenopausal hormone therapy was associated with a decreased risk of coronary heart disease. Other research findings indicated that hormone therapy was also associated with a decreased risk of osteoporosis and increased bone density, although the effects of hormone therapy on actual fracture incidence had not been determined. The WHI Hormone Therapy Trials (HT) were designed to test the effects of postmenopausal hormone therapy on women's risk for coronary heart disease and hip fractures (primary analyses) and other fractures and breast cancer (secondary analyses). The effects of hormone therapy on endometrial cancer was also evaluated in women with a uterus.

Screening and Eligibility

In addition to the general Clinical Trial exclusion criteria, HT-specific eligibility criteria were focused on safety (e.g., no history of hypertriglyceridemia or endometrial cancer, normal mammogram) and adherence (e.g., willingness to be randomized to active or placebo arms). All participants who were eligible for and interested in the HT were dispensed a 28-day supply of placebo study pills for an enrollment (run-in) trial, which could be repeated once. An adherence of 80% or greater during the enrollment period was required for eligibility.

Baseline Characteristics

The HT consisted of two separate clinical trials in postmenopausal women ages 50 to 79 years at baseline—a trial of combined estrogen and progestin (Estrogen plus Progestin or E+P) in women who had an intact uterus at baseline (n=16,608) and a trial of estrogen (Estrogen Alone or E-Alone) in women who had a prior hysterectomy at baseline (n=10,739). When the WHI began in 1993, women with a uterus were also randomized to unopposed estrogen or a placebo, but those participants assigned to active treatment were reassigned to combined estrogen plus progestin in early 1995. Baseline characteristics of participants in E+P and E-Alone trials are available in the HT baseline monograph.

Early Stopping

Following a WHI Data and Safety Monitoring Board (DSMB) review of the cumulative data to date, the E+P trial was stopped early in July 2002, after an average of 5.6 years of follow-up. The DSMB determined that combined estrogen plus progestin was associated with an increased risk of breast cancer, some increased risk of cardiovascular disease, and more harm than benefit overall. The Estrogen-Alone trial was stopped early in March 2004, after an average of 7.1 years of follow-up, because an increased risk of stroke was found with no benefit for coronary heart disease. The National Institutes of Health determined that follow-up for the remaining years would not change these overall findings and it would not be appropriate to expose healthy women to this risk in a prevention trial.

Estrogen plus Progestin Trial

Participants with an intact uterus at baseline were randomized in a 1:1 fashion to one of two arms:

- Combined hormone therapy, consisting of 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate daily (Prempro, Wyeth Ayerst, Philadelphia, PA)
- Daily placebo pill

Estrogen-Alone Trial

Participants with a history of hysterectomy at baseline were randomized in a 1:1 fashion to one of two arms:

- Unopposed estrogen therapy, consisting of 0.625 mg of conjugated equine estrogens (Premarin, Wyeth Ayerst, Philadelphia, PA)
- Daily placebo pill

Follow-Up Data Collection

Hormone Therapy Trial participants were followed up six weeks after randomization to address management (e.g., symptoms and adherence) and safety issues and then semi-annually for health-related outcomes and management and safety issues. Clinic visits were conducted annually, during which additional physical and gynecological examination data were collected and reviewed for safety concerns. If symptom or safety concerns (e.g., vaginal bleeding, breast changes) or adherence challenges (e.g., difficulty remembering to take study pills) were noted, these concerns were evaluated and addressed during participant contacts by trained clinicians and followed-up as appropriate.