The Women’s Health Initiative (WHI), conducted between September 1993 and October 1998, included postmenopausal women aged 50 to 79 years old from 40 US clinical centers. This groundbreaking trial completely shifted the thoughts of primary and secondary prevention of heart disease in women.

With estrogen therapy, there is an increase in the high-density lipoprotein cholesterol (HDL-C), which is protective to the coronary arteries. This mechanism and the potential benefits on the endothelium and many observational studies initially suggested that hormone therapy (HT) was protective against heart disease. The WHI enrolled postmenopausal women with and without a hysterectomy and randomized them to receiving HT. The negative results of this trial changed the face of how women are treated today.

The WHI included over 27,000 postmenopausal women; 10,739 had a hysterectomy and were randomized to conjugated equine estrogens (0.625 mg) or placebo and 16,608 postmenopausal women who had not had a hysterectomy were randomized to estrogen plus medroxyprogesterone acetate (2.5 mg) or placebo.

After the 15 years of follow-up in the combination HT group, there was an increased risk of myocardial infarction (MI), cerebrovascular accidents, venous thromboembolism and breast cancer. Physicians need to consider breast cancer risk discussed by Peter F. Schnatz, DO, on page 3. In the estrogen alone group, there was also an increase in cerebrovascular accidents. After the release of the results in July 2002, HT received a black box warning regarding their potential for increasing cardiovascular risk.1,2

Multiple substudies have been performed since the derandomization in 1998, including the age of which HT is begun, the duration of time given, the delivery mechanism and individuation in prescribing HT. Patients are seen as individuals with their risk profile analyzed before starting on HT. For example, women with multiple risk factors of heart disease should not be given HT for menopausal symptoms because the risk would be too significant. Identifying those women at risk includes looking at the traditional risk factors such as hypertension, HDL-C and low density lipoprotein cholesterol (LDL-C), diabetes, smoking, family history and obesity.

During a subgroup analysis, it was noted that the age of initiation of HT was an important variable in outcomes. In fact, it suggested that there was a nonsignificant reduction in risk of coronary heart disease (CHD) in women aged 50 to 59 years in the trial of estrogen alone3 or in women with less than 10 years since menopause in the trial of estrogen plus medroxyprogesterone.4

When analyzed further, the risk of cerebrovascular accidents persisted in both of these subgroups.5,6 Identifying the age to
begin HT appears to be an important aspect in determining the risk of heart disease. As a primary prevention strategy for the development of coronary artery disease, clearly there is no role for HT. However, for the classic vasomotor symptoms that often accompany the perimenopausal period, such as hot flashes and night sweats, HT may play a role, especially in the younger population.

Age of onset of HT in relation to menopause seems to be the key to risk. As discussed, risk appears to be lower in the women ages 50 to 59 not only in cardiovascular disease, but also in total mortality. There was a progressive increase in risk for women for each decade postmenopausal, with the hazard ratio increasing not only 10 years after menopause but even more 20 years after menopause. This trend was significant only for cardiovascular disease, but not for cerebrovascular accidents.

In postmenopause, the effect of HT on cerebrovascular accidents was similar in all age groups. However, for those past menopause less than 10 years, HT did not affect cardiovascular disease risk or total mortality. The risk of cerebrovascular accidents increased only in the 50-to-59-year-old age bracket. As it was shown in the original trial, estrogen alone appeared to be associated with a lower risk of coronary artery disease than estrogen plus medroxyprogesterone.7

In evaluating a woman as a candidate for HT, screening and treatment of risk factors should be paramount. A risk/benefit ratio needs to be assessed, and those who do have multiple risk factors or are 10 or more years beyond menopause need to be excluded as candidates. Also, those women using conjugated equine estrogen and medroxyprogesterone acetate had an increased risk of breast cancer. Therefore, a woman’s individual risk of breast cancer needs to be considered.

In women over the age of 70 or who are 20 years past menopause, there is not only an increased risk of heart disease and stroke but also an increased risk of venous thromboembolism and breast cancer. Clearly, there is no role of HT in this group.

Vasomotor symptoms in menopause are the predominant reason for using HT. These symptoms in women who recently entered menopause are due to a healthy response of normal functioning blood vessels with normal endothelium in response to the shifts in estrogen. Women who have these symptoms tend not to have multiple risk factors for heart disease. Also, these reactions imply that the endothelium is functioning normally. In the older population or those with persistent symptoms of flushing and sweating, these symptoms become issues of greater concern. Over time, they signify risk factors for cardiovascular disease.

In older women with vasomotor symptoms, there tends to be cardiovascular heart disease risk factors showing that the endothelium is not functioning properly. For women with multiple risk factors or established coronary artery disease who are multiple years beyond menopause, these vasomotor symptoms may be associated with an increased risk of heart disease.

The timeframe for using HT also becomes important in determining who is a good candidate. On average, women received treatment for four to five years. When HT is used to treat patients with vasomotor symptoms, this duration is much longer than most women actually would need for treating such symptoms. Within this timeframe, the subset of WHI did show that although there was not a reduction in cardiovascular risk, researchers observed a total reduction in mortality in women aged 50 to 59 years old. This analysis of reduced mortality in this subsegment implies that HT in the short term is not necessarily harmful, but with time and with worsening vasomotor symptoms, there could potentially be an increased risk of heart disease and, therefore, HT should never be used for the prevention of cardiovascular disease.8

To further stratify risk of heart disease in this seemingly low-risk population of women ages 50 to 59 years old, an analysis was done looking at the coronary artery calcium score. For 1,064 women, researchers carried out studies looking at calcified plaque in the coronary arteries. Calcification is associated with plaque formation and is predictive of future cardiovascular events. After an average of 8.7 years after randomization, women receiving estrogen had a lower prevalence and quantity of coronary artery calcium than those receiving placebo. There appears to be a reduced plaque burden in the coronary arteries and a reduced prevalence of subclinical coronary artery disease, which helps to substantiate the hypothesis that estrogen therapy may have cardioprotective effects in younger women.9

Risk of negative events seems to be dependent on not only the postmenopausal age, but also on the type of hormone replacement used. For all women, hormone therapy failed to reduce the overall risk of cardiovascular disease, yet there was lower risk in the cohort taking estrogen alone compared to those taking estrogen plus medroxyprogesterone.

In a Danish observational study looking at women aged 51 to 69 years old from 1995 to 2001, researchers found that the type of hormonal delivery and the HT regimen made an impact on the cardiovascular risk. In fact, the highest risk of MI was found with a continuous combined HT regimen, leading to a 35% increased risk of heart attacks compared to those women who had never taken HT.

Those women who took hormones on a cyclical basis—estrogen every day with 7 to 10 days of progesterone each month—had a much reduced risk of heart disease. On the other hand, there was no increased risk of MI with unopposed estrogen, cyclical combined HT and there was also a significantly lower risk of MI found with dermal routes of application. Researchers also have noted a reduction of MI by 38% if the method of taking estrogen was via a patch.
or gel and a 44% reduction in MI if there was a vaginal application.10

Much controversy has existed in the “natural HT,” or bioidentical hormone therapy—individually compounded hormones that are chemically identical to those secreted. Three different estrogens may be used in bioidentical HT: estrone, estradiol and estriol.

Estroline is the most prevalent estrogen circulating in postmenopausal women, whereas estradiol is found in higher concentrations in premenopausal women. Estradiol is considered to be the most potent estrogen and estriol the least potent. Some have considered estriol as a safer estrogen for HT.

Bioidentical HT uses the progesterone naturally found in the body instead of the synthetic progestin medroxyprogesterone acetate found in many commercially prepared HT products. According to a statement from the American College of Obstetricians and Gynecologists, there is no scientific evidence to support these regimens; these compounds have not been approved by the FDA and bioidentical HT may confer the same risks as conventional HT.11

**Final notes**

In summary, WHI was the groundbreaking trial which demonstrated the role of HT as a treatment for symptoms of menopause, rather than as a prevention strategy for heart disease. In fact, HT increased the risk of cardiovascular disease and stroke.

Recent substudies have demonstrated the way in which HT may be used safely in female patients. These substudies have provided safety parameters to best prescribe hormone replacement therapy by time, duration and delivery.11

**References**


