Hormone Replacement Therapy (HRT) a new start to life; a magic treatment that prevents aging. Hormone preparations (estrogens with or without progestogens) have been used since the seventies. Women have been willingly taking them despite knowing some of their ill-effects such as deep vein thrombosis and gallstones. Most believed that the benefits by far outweighed the risks. Attitudes have to be re-thought with the early termination of one of the trial arms of the Women’s Health Initiative (WHI) that was evaluating hormone replacement therapy (HRT).1

**Accepted facts.** We first need to reevaluate the evidence in favor of the use of HRT. There does not seem to be any dispute regarding short-term use for relief of climacteric symptoms. There is strong evidence from randomized trials that HRT relieves hot flushes and that women who have severe symptoms experience immediate benefits.2 There is also sufficient evidence that estrogen inhibits age related loss of bone in women after the menopause. It reduces the risk of vertebral fracture by approximately 50% and hip fracture by 25-30%.3

**Women’s health initiative.** To address the balance of benefit versus risks of long-term use, the Women’s Health Initiative (WHI) was established. This massive study involves a total of approximately 160,000 postmenopausal women between the ages of 50 and 79 years, of whom approximately 100,000 are included in an observational study and approximately 55,000 in various interventional trials. The first component is the evaluation of low-fat diet in preventing breast cancer. The second component evaluates 2 HRT regimens. The first is in hysterectomized women using estrogen alone versus placebo. The second is for women with an intact uterus using conjugated equine estrogen at a dose of 0.625 mg per day in combination with 2.5 mg of medroxyprogesterone acetate versus placebo. The 3rd component of the trial evaluates the efficacy of calcium and vitamin D in preventing fractures.4

**New evidence.** On May 31, 2002, after a mean of 5.2 years of follow-up, the trial arm evaluating estrogen plus progestogens versus placebo was stopped due to an excessive number of cases of: breast cancer (hazard ratio [HR] 1.26, and major cardiovascular events namely, coronary heart disease (CHD): HR 1.29; stroke: HR 1.41; pulmonary embolism: HR 2.13. The excess numbers of thrombotic events in the trial emerged early and persisted throughout the study. The excess number of cases of breast cancer emerged after 3-4 years with increasing risk with prolonged exposure. This is consistent with epidemiologic data that showed an overall increase in risk by a factor of 1.35 with HRT use for more than 5 years.5 Some positive findings of the WHI study were: fewer hip fractures with a HR of 0.66 and colorectal cancers (HR 0.63). The reduction in fractures, including hip fractures, is noteworthy and consistent with data suggesting a decrease in the rate of osteoporosis. It must be noted that the women treated in the WHI study were older than most women using HRT. In addition, the combination product used in this study was for continuous use in contrast to the cyclical products in common use in peri-menopausal women.

**Why the difference.** Perhaps the trial results may be surprising to some, given that the findings of excess numbers of cases of CHD are in sharp contrast to the results of observational studies that claimed large reductions (by approximately half) in the risk of CHD with prolonged use of HRT.6 These had led to a large increase in the prescription and use of HRT worldwide as it outweighed the increase in breast cancer and deep vein thrombosis recognized in previous studies.7 Such a contradiction between observational and randomized controlled studies on the subject led to the reevaluation of...
the value of previously carried out smaller randomized studies that showed an increase in CHD risk with HRT. A meta-analysis of several small studies, a recent study of secondary prevention, a study of progression of atherosclerosis and a study in stroke patients all showed no benefit for HRT. A recent study on women with proven ischemic heart disease showed an increase in cardiac events in those on HRT compared to those not on it.

The future. The WHI is continuing a parallel study of estrogen alone compared with placebo in women who have undergone hysterectomy. A similar study is ongoing in the United Kingdom and there is a major study evaluating raloxifene, which is a selective estrogen receptor modulator (SERM). Given the findings of the WHI and with the similar hormonal effects of all these preparations we cannot assume they are safe until proven so. There is already evidence that SERMS increase the risk of venous thromboembolism. Alternatives to HRT for the treatment of hot flushes, including selective serotonin reuptake inhibitors or diets high in phytoestrogens, have not been evaluated in long-term studies so their risks and benefits during 2-4 years of therapy are uncertain. For the time being it may be prudent to follow the recommendations of the chief medical officer in the United Kingdom. The results from the WHI study do not necessitate any immediate changes to women's treatment. However, women on HRT should have their therapy and health regularly reviewed. Initiation of HRT should be based on review of the risks and benefits of treatment for the individual woman. The Committee on Safety of Medicines (CSM) noted that the absolute risks from HRT were small and that the overall rates of deaths and all cancers were not increased with combined HRT. The balance of risks and benefits of HRT for its licensed indications remains favorable.

References