Before 1998, Conventional held that menopausal hormone therapy (MHT), estrogen treatment in particular, provided protection against development of cardiovascular disease. This convention was based on biological plausibility provided by animal (4) and human studies (12, 14) and on findings in several large observational and epidemiological studies indicating that women taking hormones for symptoms of menopause in long-term follow-up (up to 25 yr) had a lower incidence of cardiovascular disease than their counterparts who did not use hormones (1, 2, 5–7, 10, 15, 16, 18). However, results of observational studies were criticized because they did not account for healthy user and surveillance bias and thus might not be applicable to the general population (16). Therefore, the medical and scientific communities awaited outcomes of randomized clinical trials, today’s gold-standard for evidence-based medicine, to validate these beliefs.

The first such trial, which challenged conventional thinking about the use of hormone therapy to treat cardiovascular disease, was the Heart and Estrogen Replacement Study (HERS) (9). This trial was a secondary prevention study of the effectiveness of estrogen to reverse or slow progression of disease in postmenopausal women (mean age of 67 yr) with a documented history of coronary heart disease (CHD). Estrogen treatment did not provide benefit to those women and instead increased CHD events in the initial year of treatment. Results from HERS were used as evidence against prescribing hormones for women with existing CHD. However, the question of use of estrogen for primary prevention of CHD remained open.

In the summer of 2002, a large-scale randomized trial, the Women’s Health Initiative (WHI), which was designed as a primary prevention study, also failed to validate results of observational studies. On the contrary, the WHI showed that use of a specific hormone therapy (PremPro, 0.625 mg of conjugated estrogens with 2.5 mg of medroxyprogesterone acetate) did not prevent cardiovascular disease and may have increased the rates of heart attack and stroke (19). While millions of women and their physicians wondered what to do next, the scientific community wondered what went wrong, based on a reluctance to simply dismiss results of multiple independent large observational studies as false. In addition, results from basic science experiments pointed to beneficial vascular effects of estrogen, including increased circulating high-density lipoproteins; increased production of the vasodilator nitric oxide; decreased production of the vasoconstrictor endothelin-1; downregulation of angiotensin converting enzyme; and decreased migration and proliferation of vascular smooth muscle cells at sites of vascular injury (for review, see Refs. 12, 14).

But was the WHI really a primary cardiovascular prevention study? On closer comparison of characteristics of participants of observational studies with those of the WHI, it becomes apparent that women enrolled in the WHI were several years older at initiation of MHT (average age 63 yr) compared with women of the observational studies (average age range 40–55 yr). However, in the WHI cohort, women who were more recently menopausal had a lower risk of adverse events than those who were a greater number of years past menopause (11). Thus this analysis provided a suggestion that time since menopause (menopausal age) with perhaps accompanying subclinical atherosclerosis rather than chronological age may represent important variables influencing cardiovascular effects of MHT.

The concept that time since menopause and stage of atherosclerosis may influence cardiovascular actions of estrogen has support from the basic science literature. In a series of elegant experiments conducted on primates, development of atherosclerotic plaques resulting from consumption of a moderately atherogenic diet was reduced when estrogen treatment was initiated immediately following ovariectomy. However, if treatment was delayed for 2 yr past ovariectomy (comparable to ~6 yr for women), lesions were not reversed or reduced by estrogen treatment (13). Delaying initiation of hormone treatment allows time for significant atherosclerotic plaque to develop and likely reflected the vascular condition of women enrolled in the WHI. The hypothesis that early initiation of hormone therapy, in women who are at the inception of their menopause, will delay the onset of subclinical cardiovascular disease in women is an open question and requires rigorous testing.

Another possible factor contributing to the difference in cardiovascular outcomes between the WHI and observational studies is that the formulation of estrogen differed among studies. For example, procoagulant effects of oral hormone therapy, as was used in the WHI, may not be present if estrogen were delivered to the systemic circulation by a transdermal route. These two design characteristics, early intervention and comparison of delivery route for estrogen form the rationale behind the Kronos Early Estrogen Prevention Study, or KEEPS (Fig. 1; keepstudy.org).

KEEPS is a multicenter, 5-year clinical trial that will evaluate the effectiveness of oral (0.45 mg) conjugated equine estrogens, weekly transdermal estradiol (both in combination with cyclic oral, micronized progesterone, 200 mg for 12 days each month), and placebo in preventing progression of carotid intimal medial thickening and preventing the accrual of coronary calcium in women aged 42–58 yr who are within 36 mo of their final menstrual period. KEEPS will enroll a total of 720 women in 2005–2006, with an anticipated closeout of the trial in 2010–2011 (8).

There are some important points to be taken from previous hormone replacement trials. First, findings from basic science studies can be critical in design of clinical trials, and basic scientists can be integral members of interdisciplinary clinical research teams, as is exemplified by the KEEPS. A National Institutes of Health Roadmap Initiative provided nearly $8 million in fiscal year 2004 to train clinical researchers in multidisciplinary research [http://nihroadmap.nih.gov/clinical-research]. The goal of this initiative was to accelerate and strengthen the clinical research process and hasten development of more cost-effective and targeted preventive, diagnostic, and treatment strategies for the public. Basic scientists should be encouraged to take advantage of these cross-training experiences.
Hypothetical Rationale for KEEPS

Fig. 1. Schematic of the hypothetical rationale for the design of the Kronos Early Estrogen Prevention Study (KEEPS) based on studies of nonhuman primates. Initiation of hormone therapy (HT) early in the menopause will prevent the development of atherosclerotic lesions. In contrast, initiation of hormone treatment many years past menopause or in the presence of existing disease, as was characteristic of women enrolled in the Heart and Estrogen Replacement Study (HERS) for secondary prevention of cardiovascular disease and some women in the Women’s Health Initiative (WHI) for primary prevention of cardiovascular disease, will not be able to reverse existing complicated plaque. Rather, hormone treatment at that later stage may render complicated plaques unstable through upregulation of matrix metalloproteinases (MMP-9) at plaque edges, making them vulnerable to rupture. (Revised and reproduced with permission from Ref. 3).

opportunities, and clinical scientists should be open to perspectives and participation from bench researchers.

A second point to be taken from earlier hormone replacement trials is that there is a place for critical evaluation of results of even the largest and most rigorously designed clinical trial. As W. A. Silverman summarized in an analysis of one of the earliest multicentered randomized trials conducted in the United States, “...a single exercise usually marks the beginning, not the end, of a long search for a practical solution to a complicated medical problem” (17).

Heart disease is the greatest single killer of women, accounting for 45% of total mortality (vs. ~5% for breast cancer). Osteoporotic bone fractures, for which menopausal estrogen treatment is a documented preventive option, account for significant additional morbidity and mortality. If the conclusion of the WHI that menopausal hormone treatment is not cardioprotective is inapplicable to newly menopausal women, many millions of women may endure cardiac events and bone fractures that could have been prevented as the “baby boom” generation transitions menopause. In that regard, the WHI marked a beginning and not the end of a long search for a practical solution to a complicated medical problem.

REFERENCES

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