

## Hormones To Prevent Coronary Disease in Women: When Are Observational Studies Adequate Evidence?

For many years, observational studies have reported that postmenopausal women who use estrogen have a lower rate of coronary heart disease than women who do not. Results of the Nurses' Health Study concerning this question were first published in 1985 (1) and were updated in 1991 (2), 1996 (3), and again in this issue (4). The main findings have not changed: Postmenopausal women who are current users of estrogen or estrogen plus a progestin have about a 40% lower risk for coronary disease compared with women who never used hormones. Many other observational studies have reported similar results (5), but the findings of the Nurses' Health Study carry particular weight, since it is large (70 533 postmenopausal women), is methodologically sound, and provides extended follow-up (20 years).

The association between postmenopausal hormone use and lower coronary risk has most of the elements that epidemiologists look for to suggest causation: a strong association that is consistently observed in different populations and plausible biological mechanisms, including beneficial changes in levels of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (6), improved endothelial function (7), and less progression of atherosclerosis in animals (8). However, the current report from the Nurses' Health Study documents the absence of some elements that are generally thought to support causation, such as dose-response and duration-response effects (4). No increase was seen in the apparent benefit of postmenopausal hormone therapy with increasing doses of estrogen, although a dose response is clearly observed for the beneficial effects of estrogen on lipids (9). Longer duration of hormone use was associated with less coronary benefit than short-term use in the Nurses' Health Study; the relative risk increased from 0.4 for less than 1 year of current use to 0.7 for 10 or more years. Neither of these new findings is fatal to the thesis that hormone replacement therapy prevents coronary heart disease, but they are not supportive.

As in previous reports from the Nurses' Health Study, risk for ischemic stroke was increased among hormone users compared with never-users. Other observational studies have had mixed results, and a meta-anal-

ysis of this question found no clear effect of hormone use on risk for stroke (5). Since most risk factors for coronary disease, such as age, hypertension, diabetes, and smoking, are also risk factors for stroke, it is puzzling that hormone therapy would decrease risk for coronary heart disease but increase risk for ischemic stroke. One potential explanation is that hormone therapy may have mixed effects, causing thrombotic events while improving the lipoprotein profile. Any prothrombotic activity of estrogen might have more of an adverse effect on the small vessels of the cerebrovascular circulation than on the larger vessels of the coronary circulation, and lipid lowering may be less effective in reducing risk for stroke than risk for coronary heart disease (10). Given that ischemic stroke is common in older women, the 30% increased risk among hormone users observed in the Nurses' Health Study could substantially decrease the overall benefit of hormone therapy.

Despite the fact that it is an excellent prospective cohort study, could the conclusions from the Nurses' Health Study about the coronary heart disease benefits of hormone treatment be wrong? The results of three randomized trials are very different from the findings of the observational studies. The Heart and Estrogen/progestin Replacement Study (HERS), a randomized, blinded, placebo-controlled trial of 2763 postmenopausal women with documented coronary disease, found no overall benefit of 4 years of treatment with estrogen plus progestin (11). In the Nurses' Health Study, the benefit of hormone therapy occurred soon after therapy was started, but women in HERS assigned to estrogen plus progestin had an increased risk for coronary events in the first year of the trial. The Estrogen Replacement in Atherosclerosis trial also found no benefit of postmenopausal hormone therapy. Neither estrogen alone nor estrogen plus progestin differed from placebo in effect on progression of disease measured angiographically (12). The findings of these two trials do not totally contradict those of the Nurses' Health Study, however, since participants in HERS and the Estrogen Replacement in Atherosclerosis trial had known coronary disease whereas the nurses did not. Perhaps postmenopausal hormone therapy is beneficial in

women who have not yet developed coronary disease but not in women who already have it.

Important findings from a third randomized trial make this explanation unlikely. The Women's Health Initiative randomized trial includes approximately 27 000 women without coronary disease who were randomly assigned to receive estrogen plus a progestin or placebo if they have a uterus or estrogen or placebo if they do not. The trial has completed enrollment and is now in about the third year of a planned 9-year treatment period. Recently, investigators in the Women's Health Initiative issued a press release and wrote letters to participants stating that they had observed an increased risk for cardiovascular events among the hormone-treated women in the first 2 years of the trial (13). These findings are preliminary, but they would not have been released in this manner if they were not substantial. Hormone therapy appears to be having the same initial effect on coronary risk among these healthy women as among women in HERS with documented coronary disease, and the increased risk was seen both among women taking unopposed estrogen and among those taking estrogen plus progestin.

Even the largest and best observational studies can give the wrong answer if there are unmeasured differences between the groups of women being compared. It is clear, for example, that women who take estrogen tend to be healthier and wealthier than those who do not (14). Many of these differences can be measured and controlled for in statistical analyses, but others may be difficult to measure. To be included as a hormone user, women must get a prescription for hormones, have the prescription filled, and continue to take the pills. Only a fraction of women who get a prescription ever fill it, and only 25% to 40% continue to take postmenopausal hormone therapy for more than 1 year (15). Adherence—getting the pills and taking them as instructed—may be a marker for important unmeasured differences between hormone users and nonusers. For example, in the Coronary Drug Project, a trial of the effect of lipid-lowering drugs to reduce coronary mortality, men assigned to take placebo were found to have a 40% lower 5-year risk for coronary death if they adhered to placebo treatment, compared with those who were not adherent (16). This difference persisted even after adjustment for multiple measured predictors of coronary events, including age,

blood pressure, lipid levels, and diabetes. Similar effects of adherence to placebo treatment were reported among women in the Beta-Blocker Heart Attack Trial (17). Clearly, adherence to placebo treatment is not causing this benefit but is a marker for unmeasured health behaviors that result in better coronary outcomes. The idea that the findings of large, well-conducted observational studies may produce wrong conclusions is disturbing, but this tendency toward error may chiefly afflict studies of interventions that require adherence to such therapies as vitamins, dietary supplements, medicines for prevention, and lifestyle changes.

What effect should the most recent findings of the Nurses' Health Study have on clinical practice? Given that coronary heart disease is common (about half of all postmenopausal women will develop it) and morbid (about a third will die of it), hormone therapy would be beneficial for almost all postmenopausal women if it substantially reduces risk. However, if hormone therapy does not reduce risk for coronary heart disease, adverse effects, including increased risk for venous thromboembolism (11) and, possibly, breast cancer, would require that use be restricted to treatment of women with menopausal symptoms and those at high risk for osteoporotic fractures. Despite strong observational evidence from the Nurses' Health Study and others, we believe that the disappointing results of three recent trials indicate that clinicians should not use hormone therapy for prevention of coronary disease until this practice is supported by evidence from randomized trials.

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