Diabetes and Heart Disease

Diabetes is a strong risk factor for coronary heart disease (CHD) and eradicates the usual delayed onset of fatal and nonfatal CHD in women (when compared with men) (1). Although nearly all observational studies have suggested that estrogen therapy reduces the risk of CHD in postmenopausal women (2), two large clinical trials, the Heart and Estrogen/Progestin Replacement Study (HERS) (3) and the Women’s Health Initiative (WHI) (4), compared daily conjugated equine estrogen plus medroxyprogesterone acetate with placebo and found an early increased risk of CHD and no evidence of long-term benefit. In HERS, a trial conducted in 2,763 women with known CHD, 19% were treated for diabetes at baseline. In WHI, a trial conducted in 16,608 women largely free of CHD at baseline, 4.4% were treated for diabetes at baseline. These subgroups were large enough to test for an interaction of hormone effects by diabetes status; these analyses showed no differential CHD risk or benefit among women with versus without diabetes in the HERS (5) or WHI (6) clinical trials.

These clinical trial results are in direct contrast to those reported by Newton et al. (6) in this issue of *Diabetes Care*, who report in yet another observational study that estrogen has a cardioprotective effect in women with diabetes. In this case-cohort study from a health maintenance organization (HMO), women with known diabetes who were current users of hormone therapy (with or without a progestin) had about half the risk of fatal and nonfatal CHD compared with diabetic women who had never used hormone therapy. Newton et al. also report an increasing benefit with increasing duration of use, a dose-response effect not available from their previously published case-control study (7) of CHD and hormone use in women with diabetes.

Given the null effect of hormone therapy on CHD risk in women with or without diabetes in the two large clinical trials previously mentioned, reactions to yet another observational study suggesting cardiovascular benefit are likely to be mixed. How can this observed benefit be explained? Is there more to be learned from additional analyses of observational studies of hormone therapy and CHD?

There are notable limitations to observational studies of CHD in women who use postmenopausal estrogen because hormone users are already at lower risk for CHD than nonusers. The preferential selection of “healthy/wealthy” women to receive hormone therapy is a strong bias that might explain the CHD benefit reported in observational studies. Newton et al. studied women from an HMO who were assumed to have equal access to health care; but even in this setting, those who are prescribed estrogen and take it differ from those who do not. For example, Ferrara et al. (8) reported that women from another HMO who had diabetes and were taking estrogen had significantly more education, lower rates of smoking, higher rates of regular exercise, and more frequent testing of capillary glucose than women with diabetes who were not taking estrogen. This healthy-woman bias would make estrogen appear cardioprotective, even if it was not.

The importance of this bias in explaining observational results that conflict with trial results was highlighted in a recent systematic review of observational studies performed for the U.S. Preventive Services Task Force. In this meta-analysis, cardiovascular disease rates were lower in hormone-using women, but these differences disappeared when the authors adjusted for favorable baseline differences in lifestyle or social class and education in hormone users versus nonusers (9). Only randomized clinical trials can control for both known and unknown biases.

Another potential limitation of observational studies is differential study entry or loss to follow-up by health status. This possibility is not directly addressed in the study by Newton et al. but is compatible with their surprising observation that two-thirds of the diabetic women in their cohort had diagnosed diabetes for <6 years and almost 40% had a duration of diabetes <1 year despite their average age of 68 years. Was there selective loss of less healthy HMO members with diabetes?

Another limitation of the case-cohort design is that during the era when these cases were collected (1986–1992), the package insert for conjugated equine estrogen therapy cautioned against its use by women with diabetes, hypertension, or heart disease. In a representative sample of the U.S. population studied from 1988 to 1994, postmenopausal hormone therapy was reported by half as many women with diabetes as by women without known diabetes (10).

Given the unfavorable effect of hormone therapy on CHD in women with or without diabetes in HERS and WHI, it seems likely that the results of Newton et al. are spurious consequences of biases related to the health advantage characteristics of women who use presumably preventive medications.

Given the likelihood of bias, can anything new be learned from observational studies of hormone therapy? Are there potential advantages to observational studies over clinical trials for the study of hormone treatment and CHD?

One putative advantage is the broader socioeconomic and ethnic range of women in observational studies than in clinical trials. This may be only a theoretical advantage. A 1998 national survey of women living in the U.S. found that a higher level of education, higher level of income, and being Caucasian were each associated with an increased likelihood of being provided counseling about postmenopausal hormone therapy (11).

Another potential advantage of observational studies is that they include women whose hormone therapy was initiated for severe menopausal symptoms; women with severe symptoms are typically excluded from clinical trials to reduce subsequent unblinding and dropouts. Observational studies may determine whether long-term cardiovascular benefit does occur in women who have severe hot flashes, which is a plausible hypothesis if women with severe menopause symptoms also have very low estradiol levels that were corrected by hormone therapy. Such a thesis could not be readily tested in a clinical trial. Also, pooled observational studies of current
hormone use might include enough women who began estrogen <1 year after their last menstrual period to determine whether estrogen is cardioprotective if initiated during or even before the menopausal transition. Testing the possibility that estrogen has a cardioprotective effect only when begun in the perimenopause would require a very large clinical trial with CHD outcomes, which could not be seriously considered without supporting evidence from observational studies.

Finally, observational data could test the claim that “the real women seen in practice” (i.e., women in observational studies) receive individualized treatment instead of the single, standard dose regimen typically used in a large clinical trial. It seems unlikely that individualized treatment explains the more favorable results in observational studies because >80% of women in these studies used 0.625 mg of conjugated equine estrogen alone or with cyclic medroxyprogesterone acetate. Nevertheless, outcomes by treatment regimen could be examined using verified medication data from computerized HMO pharmacy records, including hormone type, dose, and duration and most recent use.

I believe that little more will be gained from observational studies of hormone treatment and clinical CHD. Observational studies may be useful to study questions that cannot be addressed in clinical trials, such as those described above. Further studies of CHD outcomes by selected phenotypes and genotypes in populations may ultimately elucidate CHD benefit or harm consequent to postmenopausal hormone use.

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References