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EDITORIAL COMMENT

New Hope for Hormone Replacement and the Heart?*

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In this issue of the *Journal*, Lindenfeld et al. (1) report an analysis examining the association between postmenopausal hormone replacement therapy (HRT) and survival in women with moderate to severe heart failure (HF). The data in the analysis are derived from the Beta-Blocker Evaluation of Survival Trial (BEST), which was a randomized trial that compared the effect on survival of a nonselective beta-blocker, bucindolol, with that of placebo in men and women with moderate to severe HF (2). In the 435 women who were 50 or more years of age, the adjusted probability of survival 42 months after study entry was 58% in non-users of HRT and 78% in users. These results are consistent with those of Reis et al. (3), who examined the association of postmenopausal HRT with survival in women with advanced HF based on pooled data from three trials comparing vesnarinone with placebo. In the Reis et al. (3) analysis, 12 months after entry, survival was 73% in 897 women who were non-users of HRT and 85% in 237 users of HRT.

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Until five years ago, postmenopausal HRT appeared to hold great promise in the primary and secondary prevention of coronary heart disease. Widespread use of postmenopausal hormones for "heart health" was based on data from observational studies that showed lower incidence and mortality from coronary disease in users of HRT who were free of coronary disease and better survival in hormone users with established coronary disease (4).

The 1998 publication of the results of the Heart and Estrogen/progestin Replacement study (HERS) (5)—a randomized, placebo-controlled trial of the effect of combined estrogen/progestin HRT on coronary events in women with established coronary disease—followed closely by the publication of the results of the Estrogen Replacement Atherosclerosis (ERA) trial (6)—a randomized, placebo-controlled trial of the effect of combined estrogen/progestin therapy and estrogen alone on progression of atherosclerosis—dampened enthusiasm for hormones in prevention of coronary disease. Lack of enthusiasm turned to downright pessimism with the 2003 publication of further results from HERS (7) and, more importantly, results of the combined estrogen/progestin arm of the randomized trial component of the Women's Health Initiative (WHI) (8). This arm of WHI, which involved more than 16,000 women, was designed to test the effect of hormone replacement in the primary prevention of coronary heart disease. It unexpectedly found a significantly increased risk of coronary heart disease in women assigned to combined estrogen/progestin HRT.

In spite of this gloomy picture, hope persists that estrogen alone—where WHI results are not yet available—or estrogen/progestin combinations that were not used in WHI, or hormones initiated at ages earlier than in WHI might have a beneficial effect on some aspect of cardiovascular health (9). The data suggesting that postmenopausal hormone therapy might affect survival in women with HF are sure to fuel this hope.

How should this analysis of HF be interpreted in the context of recent findings from randomized trials of HRT? Both Lindenfeld et al. (1) and Reis et al. (3) call for a randomized trial of HRT in women with HF. Is this the best next step?

The use of data from randomized trials to explore associations with end points of factors that were not the subject of the randomization capitalizes on the collection of data on prognostic factors in HF based on standardized protocols. Other positive features of well-conducted randomized trials, such as systematic monitoring of the quality of data collection and careful verification of end points, carry over to these analyses. Notwithstanding these strengths in the data from randomized trials, the comparison of hormone users with non-users is vulnerable to uncontrolled, and even controllable, confounding.

At entry to BEST, users of HRT differed from non-users in many ways. They were younger, taller, less obese, and more likely to be white, non-Hispanic. Their HF was more likely to be nonischemic in origin, and they were less likely to have history of hypertension and diabetes. Serum creatinine, sodium, and ALT, all independent predictors of mortality in patients with HF, were all significantly lower in hormone users than in non-users. Statistical adjustment was used to try to take these differences into account in drawing conclusions about the effect of hormones on survival.

It has been suggested that "compliance bias" might explain the lower risk of coronary disease found in observational studies of hormones and coronary disease (10). Preventive behaviors differ between hormone users and non-users (11), leading to the hypothesis that "prevention bias" might explain the findings of observational studies. Lindenfeld et al. (1) attempt to eliminate compliance bias and prevention bias by including measures of health status and compliance with treatment with study medication in BEST in a multivariate analysis.

It is doubtful that a measure of health status captures fully all of the many possible differences in preventive behavior, health habits, and lifestyle between hormone users and

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non-users. Multivariate analysis does not adjust for what is poorly measured. With so many measured differences between the hormone users and non-users in BEST, there are also likely to be unmeasured differences. Multivariate analysis does not account for what is not measured. Bias due to compliance arises not from a specific behavior but from a panoply of differences that are captured by the decision to be compliant. It is no surprise that adjustment for compliance did not alter the relationship between hormone use and survival. Multivariate analysis does not adjust for what is unmeasurable. The discrepancy between observational studies and randomized trials of hormone replacement for coronary disease should teach us to be not just skeptical, but extremely skeptical, of the ability of statistical adjustment to yield valid conclusions about drug efficacy.

Lindenfeld et al. (1) provide an exhaustive review of the possible mechanisms by which exogenous estrogen or progestin might have a true biologic effect in decreasing mortality in women with HF. Absence of a mechanistic explanation for the observed association would raise serious questions about whether the observation is real. However, mechanistic arguments must be viewed cautiously in light of the randomized trials. The hormone regimens used in the randomized trials examining coronary heart disease and measures of coronary atherosclerosis have extensive data to establish a mechanism for a benefit in preventing coronary disease and delaying progression of atherosclerosis, including favorable effects on total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrinogen, and fasting insulin and glucose (12,13).

Data from both HERS and WHI show that combined estrogen/progestin HRT at least doubles the risk of venous thromboembolism (8,14), and several observational studies show that estrogen alone also increases the risk of venous thromboembolic disease (15–17). In the WHI, the risk of ischemic stroke was also increased in users of combined estrogen/progestin therapy (8). Given the high risk of venous thromboembolism and stroke in women with HF, concerns are sure to be raised about the ethics of a trial of either combined estrogen/progestin therapy or estrogen alone. Recruitment of women with HF to a trial is likely to be challenging, even if deemed ethical.

Taken together, the results of the analysis of BEST and the three vesnarinone trials do not provide much data upon which to select a regimen of hormone replacement for a randomized trial. Lindenfeld et al. (1) found no difference in survival in users of combined estrogen/progestin therapy compared with estrogen alone. The analysis of data from the vesnarinone trials found a nonsignificant trend toward less benefit of combined estrogen/progestin therapy compared with estrogen alone. The statistical power of the comparison of estrogen/progestin with estrogen alone was low in both analyses, and the data are compatible with large differences in the effect of combined therapy compared with estrogen alone.

Lindenfeld et al. (1) make much of the fact that the magnitude of the association between HRT and improved survival was greater in women whose HF was nonischemic in origin (hazard ratio 0.35) than in women whose HF was ischemic (hazard ratio 0.74). The confidence intervals (CIs) for these estimates of HRT overlap (95% CI 0.14 to 0.87 for nonischemic HF; 95% CI 0.41 to 1.33 for ischemic HF), and the claim for a difference between any effect of HRT on survival in ischemic and nonischemic HF is very tentative. Importantly, the Reis et al. (3) analysis of data from the vesnarinone trials did not find any difference in the association of HRT with survival between ischemic and nonischemic HF.

The immediate practical importance of having more clarity on this point is for the design of a randomized trial that would address the question of a possible effect of HRT on survival in women with HF. A study that includes HF of both ischemic and nonischemic etiology would need to be larger than a study of one or the other type of HF and, thus, would be more expensive. Given the results of HERS, recruitment of women with HF with an ischemic etiology to a trial of hormone replacement would perhaps be more difficult than recruitment of women with HF without an ischemic etiology.

A number of relatively recent randomized trials of HF [e.g., OVERTURE (18), ATLAS (19), CIBIS II (20), IMPRESS (21)] included reasonably large numbers of women. Analysis of data from other HF trials with information on HRT would be the most important next step to guide a decision about whether to conduct a randomized trial of hormone replacement in women with HF. Information from such analyses would permit design of the safest possible trial that would enroll women with the types of HF that are most likely to benefit from hormone use.

The HF data are a minor reprieve for hormones and the heart. Knowledge of the past suggests extreme caution, and clinical practice should not be changed based on these findings. The path from hormone replacement to cardiovascular health is littered with plausible mechanisms, elegant models, consistent data, and anguished analysts.

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