Editorial

Hormone Replacement Therapy and Heart Disease
Replacing Dogma With Data

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In 1966, Dr Robert A. Wilson wrote an influential book entitled *Feminine Forever* that extolled the virtues of postmenopausal hormone replacement therapy (HRT).[1] Over the next 3 decades, use of HRT to preserve the health and vitality of postmenopausal women became one of America's most popular medical treatment paradigms. The enthusiasm for HRT was greatly enhanced by the perception that it could lower a woman's risk for heart disease, perhaps by as much as 50%. This notion was fueled, in part, by the remarkably consistent finding from observational studies that postmenopausal users of HRT had substantially lower rates of cardiovascular events than non-users.[2] Promising in vitro and animal model studies and favorable effects of HRT on cardiovascular risk factors added credibility to the observational study findings.[3] By the mid-1990s, these cardiovascular and other data, coupled with effective relief of postmenopausal symptoms, helped make HRT the most frequently prescribed drug in the United States, despite the absence of any large, randomized clinical trials documenting its net clinical benefits or risks.

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In 1998, however, the HRT paradigm began to crumble with the release of the Heart and Estrogen/progestin Replacement Study (HERS). In this, the first major randomized clinical trial of HRT for secondary prevention of heart disease, there was no overall benefit of hormone treatment, but there was an unexpected pattern of increased risk during the first year of follow-up.[4] Since then, 7 additional randomized clinical trials, testing a variety of hormone replacement regimens, also found no benefit of HRT on anatomic or clinical manifestations of atherosclerosis in women with established cardiovascular disease.[5–9b] In many of these trials, there was a persistent suggestion that HRT might indeed increase cardiovascular risk. Debates about the validity, generalizability, and proper interpretation of these trials resulted in numerous editorials and opinion pieces in *Circulation*[10,11] and elsewhere.

Then, in July 2002, one arm of the ongoing Women's Health Initiative (WHI) HRT trial was stopped early because of greater harm than benefit in the estrogen plus progestin group. The results, derived from largely healthy normal women, included a small (in absolute terms) but statistically significant 29% increase in myocardial infarction (MI) and coronary heart disease death, a 41% increase in stroke, and a more than 2-fold increase in venous thromboembolic events.[12] These findings, along with a 26% increase in breast cancer, precipitated a rapid and dramatic transformation of the HRT paradigm. With respect to heart disease, the view of conventional HRT has migrated from a position of presumed benefit to one of proven harm.

This remarkable sequence of events has raised a number of pressing issues. One of the most important is the need to understand how it is that results from observational studies and randomized clinical trials of HRT could produce such radically different results. In this issue of *Circulation*, Ferrara et al[13] provide yet another illustration of this awkward reality. In their careful analysis of a large cohort of diabetic women from the Northern California Kaiser Permanente Diabetes Registry, current HRT use was associated with a significant 16% lower rate of fatal and non-fatal MIs. Among users of medium- or low-dose regimens, the relative hazards were even more impressive (0.81 and 0.49, respectively). Thus, on the surface, it would appear that these data are yet another example of observational data that do not reflect clinical trial reality.

Several explanations for this apparent discordance between observational studies and clinical trials have been suggested. Observational studies may be biased by the fact that HRT users are typically healthier and wealthier than non-users. However, in most major observational studies of HRT, including the effort by Ferrara et al[13], adjustment for potential confounders or use of other more sophisticated adjustment techniques[14] have failed to remove the apparent benefit. Likewise, the average follow-up of 5.2 years in WHI and the long-term follow-up of the HERS cohort (mean of 6.8 years)[15] argue against the possibility that the initial clinical trials were simply too short to document the benefits that were apparent in longer-term observational studies.

Another credible explanation for the discordance between observational studies and clinical trials is that observational studies of any chronic intervention are intrinsically biased in favor of successful long-term users of the intervention. This is a consequence of the simple epidemiological principle that the prevalence of a condition is a function of the rate at which the condition occurs (incidence) and the length of time the condition persists. Thus, in any cohort of postmenopausal women, successful long-term users of HRT will be over-rep-

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resented relative to new users; and, more importantly, users who have suffered a fatal adverse effect of HRT will be completely absent. During subsequent follow-up, the experience of the few short-term or new users will be diluted by the experience of the larger number of successful long-term users. It is only when analyses are specifically limited to short-term or new users that a balanced view of the effects of the intervention is revealed. Thus, in the Diabetes Registry subjects, there was a 16% reduction in risk among all current users; however, when the analyses were limited to new users (<12 months), there was no evidence of benefit. More impressively, among those with a recent MI, the relative hazard for a recurrent MI was 1.78 for all users, but 3.84 for new users, once again illustrating the tendency to underestimate the risk associated with HRT use when examining all current users. Similar results have emerged from reanalyses of other large cohort studies of HRT and heart disease.[16,17] Unfortunately, even in very large cohorts such as the Diabetes Registry, confidence in subgroup analyses of new users is often compromised by small numbers. For this reason, a clinical trial with adequate numbers of subjects in the test and control arms remains the preferred method to assess both the efficacy and safety of HRT or any other form of drug therapy.

The tendency for an observational study to underestimate risks of a drug is greatest when the risk occurs shortly after initiating therapy. All of the randomized clinical endpoint trials of HRT focusing on clinical endpoints have observed an early separation in the cumulative incidence curves in the direction of harm,[4,7,12] suggesting a subgroup of women who are uniquely prone to an adverse effect of HRT. What distinguishes these women from those who successfully use HRT for extended periods of time without cardiovascular complications? The data from Ferrara et al[13] add to the growing body of evidence that the state of vascular health of a woman may be one important consideration. In this high-risk group of diabetic women, the risk of HRT in absolute terms was greatest in those with a recent MI. Similarly, the absolute risk of HRT in the first few years of treatment in HERS was roughly 10-fold higher than in WHI.[4] The recognition of HRT-associated increases in CRP[18] supports the concept that HRT may induce a proinflammatory state that destabilizes existing vulnerable coronary lesions, possibly through facilitation of matrix metalloproteinase expression in the vessel wall.[19] Ironically, estrogen induction of matrix metalloproteinase expression plays a central role in the menstrual cycle and during pregnancy.[20] Thus, this effect of estrogen may be yet another feature of human biology that is adaptive for survival or reproductive success in youth, but becomes a sword of Damocles later in life. Genetic variants that modify the estrogen-associated risk for thrombosis[21] or the effects of estrogen in other domains of estrogen action[22,23] represent other important areas of ongoing research that may account for clinical heterogeneity in response to HRT.

There are at least 2 important lessons from this extraordinary story of HRT and heart disease. First, observational data, clinical studies of intermediate endpoints, and in vitro and animal-model research are useful for hypothesis generation, but they should never be considered adequate to justify a broad-based pattern of clinical practice, such as the widespread use of HRT that occurred during the last decade or more. This is especially true for chronic interventions designed to be used by large numbers of healthy individuals in the hope of preventing future disease. In the words of Claude Bernard, "Science teaches us to doubt, and in ignorance to refrain."[24] Second, the cardiovascular effects of estrogen are far more complex than initially assumed. Unraveling these effects remains an important public-health priority. Learning how it is that estrogen can have such favorable effects on lipids, endothelial function, and other aspects of vascular biology and still produce a net increase in clinical cardiovascular events will teach us something fundamentally important about cardiovascular disease that currently remains beyond our grasp. The possible utility of lower doses (as suggested by the data from Ferrara et al[13]), novel estrogen agonists, including selective estrogen receptor modulators, or use of HRT before the development of vascular disease are just a few examples of additional ideas that deserve careful attention. In short, the final chapter of this fascinating story has not yet been written.

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