The Time Has Come to Stop Letting the HERS Tale Wag the Dogma

Michael E. Mendelsohn, MD; Richard H. Karas, MD, PhD

The premise of this commentary is simple. We believe there has been enormous overinterpretation and misinterpretation of recent clinical data (the HERS tale) with regard to the efficacy of hormone replacement therapy (HRT) in preventing or diminishing the risk of heart disease (the dogma). Both the medical and lay press have focused on obtaining a single yes-or-no answer to the question, “Does postmenopausal HRT reduce the risk of cardiovascular disease (CVD)?” This oversimplified approach has led to unjustified generalizations with regard to the question and to the summary judgment in some circles that HRT is not beneficial for the prevention of heart disease.

A brief review of the literature in this area reveals the source of much of the controversy and confusion. In 1992, an elegant meta-analysis by Grady and colleagues2 concluded that “there is extensive and consistent observational evidence that estrogen use reduces risks for CHD [coronary heart disease] about 35%.” This conclusion has since been supported by additional observational studies that together include several hundred thousand woman-years of follow-up. As one example, a recent update from the Nurse’s Health Study (>400,000 woman-years of follow-up) again confirmed a 40% to 60% reduction in cardiovascular events in women taking HRT.3,4 In contrast to this large body of observational data, the recent prospective Heart Estrogen/Progestin Replacement Study (HERS) proved negative. HERS, the first prospective, randomized trial of HRT assessing cardiovascular end points, demonstrated that combined HRT (0.625 mg/d conjugated equine estrogens [CEE] and 2.5 mg/d of medroxyprogesterone acetate [MPA]) had no effect on fatal or nonfatal cardiac events.1 The study included 2763 women with established coronary artery disease followed up for an average of 4.1 years. It is largely the discrepancy between the results of HERS and the many prior observational studies that has led to the current lack of consensus about the cardiovascular effects of HRT.

On July 24, 2001, the American Heart Association released a consensus statement addressing the use of HRT in women with heart disease.5 This statement attempted, among other things, to introduce a quite specific caution (Table 1, point 1), crafted largely in response to the data from the HERS trial. Unfortunately, these recommendations were subject to almost immediate misinterpretation that began with the press release from the AHA itself the same day:

Dallas, July 24—The American Heart Association today advised physicians against prescribing hormone replacement therapy (HRT) for the sole purpose of preventing heart attacks and strokes in women who already have cardiovascular disease according to recommendations published in today’s Circulation: Journal of the American Heart Association. The new position is based on recent scientific studies about the role of HRT in reducing the risk of coronary heart disease in postmenopausal women. For postmenopausal women who have had a heart attack or stroke, the guidelines recommend that HRT not be initiated for secondary prevention. This recommendation is based, in part, on the results of the Heart and Estrogen Replacement Study (HERS), a large-scale study that found no benefit of HRT among women with heart disease.

Confusion and misinterpretation immediately followed publication of the guidelines, in part because the short statement in the summary recommendations that “HRT should not be initiated for the secondary prevention of CVD” did not adequately emphasize the word initiated. The statement also was not qualified by including the demographics of the HERS study population (ie, “. . .in women who are many years past the menopause”).5

TABLE 1. Summary Recommendations for HRT* and CVD From the AHA Statement of July 24th, 2001

<table>
<thead>
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<th>Secondary Prevention</th>
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<tr>
<td>(1) HRT should not be initiated for the secondary prevention of CVD.</td>
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<tr>
<td>(2) The decision to continue or stop HRT in women with CVD who have been undergoing long-term HRT should be based on established noncoronary benefits and risks and patient preference.</td>
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<td>(3) If a woman develops an acute CVD event or is immobilized while undergoing HRT, it is prudent to consider discontinuance of the HRT or to consider venous thromboembolism prophylaxis while she is hospitalized to minimize risk of venous thromboembolism associated with immobilization. Reinstitution of HRT should be based on established noncoronary benefits and risks, as well as patient preference.</td>
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<th>Primary Prevention</th>
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<td>(4) Firm clinical recommendations for primary prevention await the results of ongoing randomized clinical trials.</td>
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<td>(5) There are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of CVD.</td>
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<tr>
<td>(6) Initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference.</td>
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*The majority of data available to make clinical recommendations are based on standard doses of oral CEE/MPA. Evidence is insufficient to determine whether different preparations, routes of delivery, doses, or progestins have a more favorable or more adverse effect on clinical CVD end points.

Hormones for Sick Hearts. Of the major newspapers, only The Chicago Tribune attempted to stem this tide of overinterpretation with the August 1, 2001, article, “A Heart-to-Heart on HRT: Doctors Worry New Advisory Could Lead to Confusion.”

What then can we actually learn from the HERS trial? The HERS trial teaches us that women with known coronary artery disease who are ≥20 years past menopause are not protected from a cardiovascular event if they are newly initiated on combined therapy with CEE and MPA. A time-trend subanalysis of these data also demonstrated an increased risk for CHD events in the first year of therapy followed by a decreased risk for CVD events in years 4 and 5. Is this an important set of findings? The possibility that a subset of older women with known CVD may be at increased risk for a cardiovascular event if started de novo on a combination of CEE and MPA is, of course, important, and understanding the pathophysiology of this diathesis, if it proves real, likely will provide us valuable insights. The HERS data support only the conclusion that women with known CVD who are ≥20 years past menopause ought not to have HRT therapy added to their regimen. They do not otherwise alter our approach to the management of CVD in older women. In 2001, very few clinicians would consider adding HRT to the regimen of a woman with CVD who is many years past the menopause, and none should. Pundits sometimes respond to this fact with the statement, “But HERS was started at a time when the optimal approach to such patients was not at all clear.” Fine, let’s acknowledge that this is the case and then state more clearly for both the medical community and the public that HERS, formulated with the best of intentions, has little or no relevance to the way we treat CVD in women at present.

While we await additional clinical evidence about CVD and HRT, it is critical that we all emphasize the extensive data that support the beneficial effects of several nonhormonal interventions in women with CVD. For example, as most physicians know, HMG-CoA reductase inhibitors are the cornerstone of preventive therapy in men and women with known heart disease. Physicians who wish to provide state-of-the-art therapy for women with known CVD must carefully consider the use of aspirin, β-blockers, angiotensin-converting-enzyme inhibitors, and lifestyle interventions in every patient. These proven therapies, however, are still underused in women.

In part because of the HERS results, an unplanned subset analysis of the Women’s Health Initiative (WHI) study was undertaken and commented on by the National Heart, Lung and Blood Institute (NHLBI) last year. The NHLBI statement noted a trend toward an early increase in mortality in WHI subjects in the first year after initiation of HRT. This statement likely was released both as a caution in the context of HERS and as a prelude to prospective WHI substudies aimed at understanding the underlying cause(s) of any true increase in early mortality. This April 3, 2000, NHLBI statement included the comment, “This new information from WHI is considered preliminary. It does not address the larger issue of long-term benefits and risk of HRT and, therefore, it should not influence current medical practice.” Unfortunately, this advice was lost in the subsequent publicity, and the statement added to the public perception that HRT is generally bad for all women with heart disease.

Concerns about the possibility of “early harm” associated with initiating HRT have been furthered by both a recent prospective angiographic study and by retrospective analyses of existing databases. The prospective trial, the Effects of estrogen Replacement on the progression of coronary-artery Atherosclerosis (ERA) study, showed that de novo initiation of HRT does not lead to an alteration in mean minimal coronary-artery diameter measured by coronary angiography. The ERA trial has been used by some to reinforce the HERS data and to argue that HRT is detrimental to women with heart disease. However, this study, like HERS, is relevant only to postmenopausal women initiating HRT at an average of ≥20 years after menopause, which cannot be (and is not) standard practice. Furthermore, the ERA study lasted only 3 years, had no specified clinical end points, and had instead an angiographic end point that may not reflect the underlying biology of the coronary artery adequately.

A retrospective analysis of the Nurses’ Health Study appeared recently, reporting a 25% increase in major coronary heart disease events with short-term use of hormones. This publication also has been cited widely in support of the early-harm hypothesis, despite the fact that the confidence limits for this risk estimate did not reach significance (relative risk ranged from a 22% decrease to a 2-fold increase in risk). These findings are in contrast to those of Varas-Lorenzo et al, who demonstrated a reduced risk of cardiovascular events even within the first year of HRT in a retrospective case-control study of ~1200 women with myocardial infarction (MI) compared with 5000 controls.
Retrospective studies such as these highlight the very large number of individuals and clinical events that can be examined in observational and population-based clinical studies. This approach has been used carefully and advantageously in the present issue of Circulation by Shlipak and coworkers, who have examined for the first time the effect of HRT on survival of postmenopausal women after MI. In a retrospective, population-based study of the National Registry of Myocardial Infarction 3 (NRMI3), the authors note that HRT is associated with a 35% reduction in mortality for women who suffered MI in this registry. The authors also address the potential limitations of their approach with great care and apply sophisticated statistical methods (propensity scoring) to attempt to adjust for any potential residual biases. They conclude that HRT in postmenopausal women is associated with a marked reduction in mortality after MI. The group also deserves credit for the careful manner in which they qualify their conclusion, acknowledging that the finding could be the result of a therapeutic effect of HRT, selection or adherence biases, or some combination of all.

Interestingly, critics of observational data often point out the potential for observational data to be compromised by a selection bias for socioeconomically advantaged women because they are healthier and more likely to use HRT. Women on HRT in the Shlipak et al30 study were healthier on average, but they also were more likely to have a history of tobacco use and hypercholesterolemia, as well as a positive family history of heart disease, than were women not on HRT. This suggests that the aforementioned criticism of selection bias in observational studies may be more complex than has been noted previously. The 35% reduction in mortality for women on HRT who suffered MI in the Shlipak et al30 study is provocatively reminiscent of the 35% reduction in relative risk for heart disease noted in the earlier large meta-analysis of clinical HRT studies.2

It is now widely accepted that the heart and blood vessels of women and men express estrogen receptors, as well as the receptors for other steroid hormones.31 We have a number of ways to explore the significance of this fact, ranging from the most basic molecular biology approaches to cell-based and animal models, and from retrospective to prospective clinical studies. Recent data demonstrate unequivocally that both of the known estrogen receptors are important in mediating estrogen’s effects on the vascular system.32 How does the loss of circulating estrogens during menopause impact these receptors? Is the loss of estrogens related to the increase in postmenopausal risk for heart disease? Can we design beneficial therapies for heart disease directed at these estrogen receptors in the cardiovascular system? These questions, and several related ones, are complex and will require an enormous effort to answer. However, there are data from many experimental approaches to support the argument that understanding the physiology of cardiovascular estrogen receptors is a promising area of research. At present, selective estrogen receptor modulators (SERMs) are being developed by several pharmaceutical companies. It is likely that SERMs with direct cardiovascular effects soon will appear, just as the SERM raloxifene has been developed and released to treat postmenopausal bone loss.

### Table 2: General Statements Regarding HRT and CVD in 2001

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<tr>
<th>Statement</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>(1)</td>
<td>There is an enormous deficit in the public’s awareness that heart disease is the primary cause of mortality in women. This needs to be addressed in a major, proactive educational campaign.</td>
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<tr>
<td>(2)</td>
<td>Although we await the results of large, prospective, randomized trials, many observational studies support the conclusion that the use of HRT has cardiovascular benefit in healthy postmenopausal women (primary prevention).</td>
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<tr>
<td>(3)</td>
<td>The magnitude of cardiovascular benefits from HRT is likely decreased by advancing age, time since menopause, the presence of other cardiovascular risk factors, and especially the presence of known coronary artery disease.</td>
</tr>
<tr>
<td>(4)</td>
<td>In women with known cardiovascular disease who are many years past the menopause, HRT should not be initiated for the treatment of heart disease (HERS).</td>
</tr>
<tr>
<td>(5)</td>
<td>A HMG CoA-reductase inhibitor (statin), not HRT, is the drug of choice for any postmenopausal woman with hypercholesterolemia.</td>
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<tr>
<td>(6)</td>
<td>In selecting HRT, consideration should be given to the lipid profile because different HRT regimens have different effects on various lipoproteins.</td>
</tr>
<tr>
<td>(7)</td>
<td>The first-line therapies for women with known CVD include risk factor modifications, aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors, just as in men. These therapies are still underused, especially in women.</td>
</tr>
</tbody>
</table>

So, where are we left at present with regard to HRT and CVD in postmenopausal women? Perhaps the most important current need is greater appreciation of the complexities associated with understanding the cardiovascular effects of steroid hormones. These complexities include carefully noting the different compounds, dosages, patient populations, and study designs that are used in clinical research on hormone replacement as we analyze and report new studies. In addition, the fact that HRT and estrogen are not synonymous needs to be better understood because these terms continue to be used interchangeably in most circles. In practice, HRT in fact is closer to being a synonym for CEE plus MPA, although this is not the only form of HRT available at present and is itself in evolution.

When Pandora slipped off the cover of that jar she found in Epimetheus’ house, many plagues escaped before she could replace the lid, and only Hope remained at the bottom of the jar. The hope that HRT is beneficial for the primary prevention of CVD in women also remains, as it does for new SERM-based therapies directed at cardiovascular estrogen receptors, and no studies to date support otherwise. The statements in Table 2 are offered as an attempt to clarify where we stand at present with regard to HRT and CVD.

### References


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