In recent years, perceptions about postmenopausal hormone therapy (HT) have changed dramatically. Prescription rates have plummeted as HT has gone from routine to infrequent use in the wake of findings from the Women's Health Initiative (WHI) and other clinical trials. However, HT remains the most effective treatment for hot flashes and other menopausal symptoms, and recent evidence suggests that the timing of HT initiation may critically influence its benefit-risk ratio. Is the pendulum now swinging back toward moderated but judicious use? If so, how should we select appropriate candidates for HT?

In the pre-WHI era, HT was widely advocated and prescribed by the medical community for the treatment of menopausal symptoms and prevention of osteoporosis. The justification for this position was not only the efficacy of HT in reducing vasomotor symptoms and improving bone density but also evidence for cardioprotection based on observational studies. However, results of clinical trials in the last 8 years, conducted largely with older women more than a decade past menopause, have challenged the concept that HT confers cardioprotection and that its benefits outweigh its risks. Rather, trial data suggest that these medications increase or have a neutral effect on the risk for several diseases including myocardial infarction, stroke, and venous thromboembolism, whether used as single (ie, estrogen alone) or combined (estrogen plus progestin) therapy. Although HT should not be used for cardiovascular disease (CVD) prevention at any age, emerging evidence suggests that age and time since menopause modulate the effect of HT on cardiovascular outcomes.

As Dr Bairey Merz pointed out in the review article, “Hormone Therapy and Cardiovascular Risk: Why the New Focus on Perimenopausal Women?” in the June issue of *Johns Hopkins Advanced Studies in Medicine*, there are several issues that should be considered to help understand the divergent findings on hormone therapy in women. Specifically, as a result of the low sensitivity of some methods for ascertaining menopausal status, previous studies on this subject may have misclassified women with respect to estrogen levels, which may be a potent risk factor for coronary artery disease. Also, the decision to start HT may depend on the age of the woman and how far removed she is from menopause. Indeed, given the data, which Dr Bairey Merz reviews, we feel that age and time since menopause should be key clinical considerations when making the decision to start a woman on HT. This is supported by a large body of evidence that has been published previously and that is summarized below.

The observational Nurses’ Health Study (NHS) reported a 30% to 40% reduction in risk for coronary heart disease (CHD) in women who reported current use of HT compared with those who never used HT. Similar results have been found in other observational studies, which tend to include women who initiate HT within 2 to 3 years of menopause onset. These results differ from those of the WHI, a randomized clinical trial focusing on primary prevention in postmenopausal women. Compared with those receiving a placebo, women who were randomized to oral estrogen plus progestin had a significant increase in risk for CHD, stroke, and total CVD over 5.2 years of follow-up. However, when the CHD results were examined by time since menopause, hazard ratios (HRs) were found to increase with greater distance from menopause: HR = 0.89 for <10 years, 1.22 for 10 to 19 years, and 1.71 for ≥20 years since menopause. Women who were randomized to estrogen alone (CEE) did not have a significantly different risk for CHD or total CVD compared with placebo after an average of 6.8 years, but they did have an increased risk for stroke. Notably, a secondary analysis of this trial found that women who were in the CEE arm and between the ages of 50 and 59 at baseline had a lower CHD risk than that of women in the placebo arm (HR = 0.56, 95% confidence interval [CI], 0.30–1.03), whereas no risk reductions were found in women aged 60 to 69 or 70 to 79. In an updated analysis, women aged 50 to 59 in the CEE arm had a statistically significant reduction in coronary revascularization (HR = 0.55, 95% CI, 0.35–0.86) and a significantly reduced risk of a composite endpoint of myocardial infarction and coronary revascularization.

Moreover, in a recent meta-analysis of 23 trials of HT that compared results in younger women (< age 60 or <10 years since menopause) versus older women, HT significantly reduced CHD events in the former but not in the latter. Odds ratios for HT and CHD were 0.68 (95% CI, 0.48–0.96) for younger women and 1.03 (95% CI, 0.91–1.16) for older women. Similar results were found in a meta-analysis of trials assessing mortality. The hypothesis that age and time since menopause importantly influence HT outcomes is further supported by a recent report from the NHS, in which women who initiated HT within 4 years of menopause had a reduced risk of CHD, but those who initiated HT more than 10 years after menopause did not experience CHD benefit.

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Because of the discrepancy between the results of observational studies and clinical trials on the issue of CVD risk conferred by HT use, important questions have been raised about the role of methodologic (study design) versus biologic (characteristics of study population, HT formulation) issues. It is biologically plausible that HT could reduce the risk of CVD events, as exogenous oral estrogen lowers low-density lipoprotein (LDL) cholesterol, Lp(a), glucose, insulin, homocysteine, and endothelial adhesion molecule levels while raising high-density lipoprotein cholesterol, inhibiting oxidation of LDL, and improving endothelial function. On the other hand, CEE has been associated with increases in triglycerides, coagulation factors (factor VIII, prothrombin 1 and 2), C-reactive protein, and matrix metalloproteinases. Furthermore, concomitant administration of a progestin attenuates some of the beneficial effects of oral estrogens. Therefore, the effects of HT on biomarkers for CVD are complex and do not lend themselves to definitive conclusions about a net effect on clinical vascular events.

Extensive evidence now suggests that timing of initiation of HT may be a key determinant of the net effect on clinical CHD events. As noted above, women taking HT in observational studies typically start therapy in early menopause, whereas clinical trial participants are often randomized to hormones long after menses have ceased. For example, the majority (approximately 80%) of the women in the NHS who used HT started treatment within 2 to 3 years of menopause onset. In contrast, women in the WHI averaged 63 years of age at baseline and initiated HT an average of 12 to 16 years post-menopause. This difference in age and time since menopause is associated with a major difference in the underlying stage of atherosclerosis, a powerful predictor of future CHD events and mortality. It has been hypothesized that estrogen slows the early stages of atherosclerosis but may precipitate thrombosis and plaque rupture among women with advanced atheroma. Thus, the prothrombotic and proinflammatory effects of estrogens may manifest themselves predominantly among women with complex atherosclerotic lesions who initiate HT well after the menopausal transition. Women with normal or relatively intact endothelium who start HT early in menopause may derive cardiovascular benefit because they have not yet developed advanced atherosclerotic lesions. Nonhuman primate data support this idea. Conjugated estrogen had no effect on the extent of coronary artery plaque in cynomolgus monkeys assigned to estrogen alone or to estrogen combined with medroxyprogesterone acetate starting 2 years (about 6 human years) after oophorectomy and well after the establishment of atherosclerosis. On the other hand, administration of exogenous hormones immediately after oophorectomy, during the early stages of atherosclerosis, reduced the extent of plaque by 50%.

The duration of treatment with HT may be another factor leading to divergent findings between the studies, as women in observational studies tend to have longer duration of HT use than those in the clinical trials. Among WHI participants followed for the longest periods of time (ie, >5 years in the estrogen-progestin arm and >6 years in the estrogen-alone arm) there was a similar trend toward reduced risk of CHD events. The aforementioned metaanalysis of HT trials also documented differences in CHD effects according to duration of treatment.

The mixed results from different types of studies, along with the relatively small amount of trial data on HT in recently menopausal women, have led to considerable confusion amongst the medical community and the public at large. Furthermore, the complexity involved with the clinical application of divergent study results would challenge even the most seasoned clinician. Accordingly, many clinicians may feel discouraged about trying to provide guidance to their patients about HT decision making. But it’s not yet time to “throw in the towel” on HT. Recent findings provide reassurance to recently menopausal women who are considering HT for treatment of menopausal symptoms. It is possible that both observational studies and clinical trials are providing important and reliable data on HT. Specifically, there is now a critical mass of data to support a “unifying hypothesis” that age or time since menopause importantly influence the benefit-risk ratio associated with HT, especially with respect to coronary disease outcomes. The method of administration, dose, formulation, and duration of use of exogenous hormones also may be relevant. Clinically, HT remains the most effective treatment for moderate-to-severe vasomotor symptoms, which are more common in early menopause. We concur with current guidelines, also supported by Dr Bairey Merz, that the use of the lowest effective dose for the shortest duration necessary to control symptoms is appropriate. Importantly, the best candidates for HT appear to be symptomatic women who are recently menopausal and at low baseline risk of CVD. Additional research is needed to inform decision making for our patients.

References