The results of 2 large randomized trials involving postmenopausal hormone therapy (HT) recently have transformed long-standing beliefs about the efficacy and safety of such therapy in lowering cardiovascular (CV) risk. Most significantly, the landmark Women’s Health Initiative (WHI) study reported in 2002 that healthy women assigned to estrogen with progestin had a possible increase in coronary heart disease (CHD) compared with women taking placebo. The risks of stroke and pulmonary...
monary embolism also increased in women on HT while the breast cancer incidence rose slightly and the rates of colorectal cancer and hip fractures decreased. In the arm of this primary prevention study involving women who had had hysterectomies, estrogen alone had no effect on CHD risk. These results, when added to similar findings from an earlier secondary prevention trial of postmenopausal HT—the Heart and Estrogen/Progestin Study (HERS)—led to a dramatic drop in the use of HT in the United States.5

Today, based on these and other trials, major groups such as the American College of Obstetricians and Gynecologists, the American Heart Association (AHA), and the North American Menopause Society recommend against use of HT for the prevention of CHD or other chronic diseases.6-9 Overall, the US Preventive Services Task Force has stated that the harmful effects of unopposed estrogen or combined estrogen and progestin are likely to exceed the benefits of chronic disease prevention for most women.8 Instead, HT is offered at the smallest doses and for the shortest duration to manage specific symptoms of the menopause (eg, hot flashes, vaginal function) or to reduce the risk of osteoporosis. Given the net unfavorable or neutral risk/benefit profile emerging from WHI and other randomized prevention trials, this recommendation for narrowly defined use of HT in postmenopausal women remains essential guidance for the primary care physician.

Beyond the immediate impacts on clinical management of women at risk of heart disease, the new data also raise fundamental questions about both the past and future of HT in clinical medicine. Most broadly, the data force us to ask: Why are these results from randomized clinical trials so directly at odds with expectations based on decades of observational studies? Observational data, after all, have consistently demonstrated a lower risk of CHD in young (premenopausal) women than in age-matched men.10-12 Observational studies also have suggested that CHD risk rises following the menopause10,11 and, further, that CHD risk is higher in young women undergoing premature menopause compared with age-matched women.11,12 In terms of hormone replacement, the epidemiologic data also suggested a decreased risk of CHD associated with HT.13-14 A meta-analysis of the observational data, for example, showed that CHD mortality was reduced among current HT users (relative risk [RR] 0.62; 95% confidence interval [CI], 0.40-0.91).15 All of this evidence, plus several lines of basic science research, seemed to solidify the hypothesis that women do not develop heart disease until after menopause because estrogen protects their blood vessels. This medical hypothesis, perhaps abetted by ingrained societal beliefs and commercial practices,16 paved the way for growing worldwide use of HT in an attempt to reduce CHD risk in the 1980s and 1990s. Then came the shock of HERS and WHI.

What might explain this reproductive hormone paradox? Some of the discrepancies between the observational data and the randomized clinical trial data are clearly related to uncontrolled variables such as more healthy women being in the HT groups of the observational studies; this “healthy user bias” can occur either by patient choice or by physician selection. In the meta-analysis of observational studies mentioned above, for example, the pooled RR of coronary artery disease (CAD) rose from 0.80 to 0.97 when data were adjusted for socioeconomic status and CV risk factors.15 Other factors may involve the inability to capture clinical events soon after treatment initiation or to account for the variability in dosing or formulation effects.17

Recently, 1 of the key factors to emerge in explaining these inconsistencies involves the woman’s age and whether the HT was given early or late in relation to the menopause. In WHI, for example, the average subject was 63.3 years of age and approximately 12 years postmenopausal. By contrast, many women in the epidemiologic studies had initiated therapy much earlier—usually at the menopause transition.18-20 In this article, we review several questions related to the potential role of age and menopausal status in HT for CHD prevention. Specifically, we ask:

• How accurately is menopause measured in women, and what is the role of menopausal status versus age in rising CHD rates in women?
• Are estrogen deficiency or androgen excess risk factors for CHD in young women?
• Is HT effective in perimenopausal women?

Emerging data from the ongoing Women’s Ischemia Syndrome Evaluation (WISE) study help provide answers to the first 2 questions. Results from 2 other very recent studies help in addressing the more clinically crucial third question. The first of these recent studies is a subgroup analysis from WHI19 and the second is a follow-up report from the large prospective Nurses Health Study (NHS).20 As detailed in this review, the new data indicate that the timing of HT in relation to menopause onset may indeed influence coronary risk. The basic and clinical research findings reviewed here, if verified in planned prospective trials of early estrogen prevention, could lead to a refinement in the way that clinicians employ HT for CV risk reduction in women.

Prevention of Cardiovascular Disease in Women: Why It Matters and Why Estrogen May Yet Play a Role

CHD is the leading cause of death for American women in the United States21 and CVD is the leading cause of admissions to short-stay hospitals.22 In 2003,
CVD killed 483,842 women whereas breast cancer claimed the lives of 41,566 and lung cancer 67,894. It might seem that the tendency for women to have myocardial infarctions (MIs) at later ages would explain why about 25% of men versus 38% of women die within 1 year after having an initial recognized MI. However, even young women seem to be at elevated CV risk. Women under 50 years of age, for example, are about twice as likely to die after an acute MI than are men in the same age group (Figure 1). Overall, while CV mortality has gradually decreased in men over the last 2 decades, it has remained relatively unchanged in women.

Because CVD so often presents as sudden death—64% of women who die suddenly of CVD have had no previous symptoms—primary prevention is crucial. The current recommendations from the AHA advocate a risk-based approach to preventing CVD with lifestyle interventions for all women and higher risk and costlier pharmacologic approaches reserved for higher-risk women. For example, in women with high blood pressure (>140/90 mm Hg) there is good evidence that pharmacologic intervention prevents future CVD. Also, aspirin or lipid-lowering medications are used in women whose 10-year risk of CVD is greater than 10%.

But even as clinicians pursue such evidence-based strategies for primary prevention, researchers continue to evaluate the complex mix of risk factors that may explain the excessive burden of CVD in women. Recent findings of elevated myocardial ischemia in premenopausal women with elevated systolic blood pressure, for example, suggest that identification of hypertension in premenopausal women should dictate more aggressive assessment and risk factor management. Other emerging evidence points to an unexpectedly lower prevalence of obstructive CAD by coronary angiography in women compared with men. And, a recent study showed that the Framingham risk score, which often is used to guide primary prevention with aspirin and lipid-lowering drugs, many times fails to identify women who are at high risk owing to family history or heart disease and subclinical atherosclerosis.

These and other results from sex-related studies of CV risk support the concept of a unique multifactorial model where sex hormones interact with traditional and conditional risk markers and lead to an increase in atherosclerosis or vascular or metabolic changes that worsen outcomes for women. These ongoing studies of the unique and, to some degree, age-dependent risk profile in women may eventually lead to changes in everyday clinical practice—for example in risk profiling with less traditional stress testing and more novel imaging, or with more consideration of possible hypoestrogenemia or inflammatory states. The information presented in the remainder of this article will address the facets of this emerging hypothesis that are related to hormone therapy and will explain why studies of early targeted intervention with estrogen are now under way.

NEW QUESTIONS RELATED TO HORMONE THERAPY

HOW DO WE MEASURE MENOPAUSE?

To compare the relative contributions of advancing age and menopause on CAD risk in women, a more accurate and consistent determination of menopause status is needed. In most large studies to date, women were deemed menopausal if they had not had menstrual flow in the previous 12 months. If the woman had had a hysterectomy and was younger than 55 years of age, she might be classified as premenopausal. These self-reported “menstrual” and “historical” algorithms are overly simplistic and not a true reflection of ovarian function. Unfortunately, more accurate classification schemes based on repeat hormone assays are not feasible in large epidemiologic studies or in clinical practice.

As a practical compromise solution, the WISE study group recently developed a simple algorithm for...
determination of menopause status that was based on a single nonfasting blood draw together with the menstrual and reproductive history. When compared with the 2 currently used methods, this new “hormonal algorithm” provided a more accurate assessment of menopausal status as determined by comparison with the gold standard of individualized expert evaluations. In 515 women, the self-reported menstrual and historical methods differed significantly from the expert consensus in 32% and 25% of the women, respectively ($P < .0001$). In contrast, the relatively simple WISE algorithm was discordant in only 4% of cases.

These results imply that traditional menopause measurements based on menstrual and historical variables have been inaccurate one quarter to one third of the time. This level of inaccuracy should concern clinicians as well as researchers, as it forces a reevaluation of longstanding conclusions—such as those based on Framingham data—about the risk of heart disease accelerating after menopause. If these older studies are inaccurate up to one third of the time, the data must be questioned.

The new WISE results confirm that improved menopause measurement is achievable with a simplified itemized questionnaire and a single blood sample. With validation of this new tool, it can now be used to generate more accurate sex-based research on CVD risk. Already, the hormonal algorithm has been used in a WISE study to demonstrate that age and menopause are practically inseparable as factors in cardiac risk. In this same study, high systolic blood pressure was identified as a greater risk factor for CAD in premenopausal versus postmenopausal women. Though further study is needed to determine if hypertension treatment guidelines should be altered for premenopausal women, the preliminary results from studies built on more accurate measurements of menopause indicate that natural menopause may not be the physiologic milestone of risk that it is still commonly thought to be for accelerated cardiac disease.

Is Estrogen Deficiency a Risk Factor for Cardiovascular Disease?

One hypothesis for explaining the greater adverse outcomes in premenopausal women compared with age-matched men with ischemic heart disease involves estrogen deficiency due to ovulatory dysfunction. Animal data have long suggested that stress will cause more disruptions of ovarian function (eg, luteal deficiency, anovulation) in subordinate female monkeys than in their dominant counterparts. Whereas the dominant primates continue to have normal cycles 88% of the time, the subordinate animals had normal cycles only 54% of the time.

Lower estrogen levels were significantly associated with atherosclerosis in these stressed animals. When the animals were treated with oral contraceptives, however, the stress-related impact on atherosclerosis was abolished.

In clinical studies, the WISE study group has now shown that estrogen deficiency also may predict obstructive CAD in premenopausal women. Reproductive hormone blood levels and angiographic CAD were assessed in 95 premenopausal women with coronary risk factors. As shown in Figure 2, the women with angiographic CAD (n = 13) had significantly lower estradiol, bioavailable estradiol, and follicle-stimulating hormone (all $P < .05$) than did women without angiographic CAD (n = 85), even after controlling for age. A multivariate model showed that hypoestrogenemia of hypothalamic origin was the most powerful predictor of confirmed CAD (odds ratio [OR] 7.4; CI 1.7-3.3, $P = .008$). Interestingly, multivariate analysis also showed that use of anxiolytic/sedative/hypnotic medications in the previous week were independent predictors of hypoestrogenemia of hypothalamic origin (OR 4.6; CI 1.3-15.7, $P = .02$) and use of antidepressants was much lower among these women (OR 0.10; CI 0.01-0.92, $P = .04$). In light of the animal data on stress, these latter results suggest that the anxiolytics and related therapies may signal the presence of stress in the women’s lives—stress that is inadequately covered up—whereas the antidepressants seem to produce a more fundamental and possibly estrogen-modulating effect. More recently, in a yet-to-be published cross-sectional observational study, the WISE researchers also demonstrated that coronary artery obstruction severity is significantly

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**Figure 2. Estrogen Deficiency Predicts Obstructive Coronary Artery Disease in Premenopausal Women**

![Figure 2](image-url)

**Legend:**

- Estradiol (pg/mL): P = .003
- Bioavailable Estradiol (pg/mL): P = .002
- Estrone (pg/mL): P = .002
- FSH (mIU/mL): P = .03
- LH (mIU/mL): P = .09

**Note:**

- FSH = follicle-stimulating hormone; LH = luteinizing hormone; CAD = coronary artery disease.
- Reprinted with permission from Bairey Merz CN, et al.©
lower in those postmenopausal women who had used oral contraceptives at some point in their past (n=264) versus those who had not (n=408) \( (P = .002) \). There were not enough women in the study to determine if the total time of hormone use affected the artery scores. Nonetheless, the tentative conclusion from these multiple lines of investigation is that estrogen deficiency in relatively young women may play a role in CVD.

**Is Hormone Therapy Effective in Perimenopausal Women?**

A range of studies have now told us with some authority that hormones do not protect against heart disease in groups of women who are mostly in their 60s. In the HERS trial, postmenopausal women with established coronary disease were randomized to either oral conjugated equine estrogen plus medroxyprogesterone acetate or placebo.4 After 4.1 years, the hormone treatment did not reduce the overall rate of CHD events. There were, however, more CHD events in Year 1 and fewer in Years 4 and 5 (Table 1). This pattern of an early increase in risk of CHD events is also found in the WHI study and, as discussed below, indicates that the duration of observation in these large trials is a key factor in trial outcomes and interpretation. In the Estrogen Replacement Angiographic (ERA) trial, both estrogen and estrogen plus progesterone produced positive effects on low-density and high-density lipoproteins but neither form of HT had any effect on the progression of CAD as measured by quantitative angiography.34 Similar angiographic results have been reported by others.35 The ERA data also showed a trend toward greater incidence of deep venous thrombosis and pulmonary embolism in the treated groups. Other trials of secondary prevention with HT such as the Women's Estrogen for Stroke Trial (WEST),36 the Papworth HRT Atherosclerosis Study (PHASE),37 and Women's International Study of Long Duration Oestrogen after Menopause (WISDOM)38 have come to the same conclusion: there is no CVD risk reduction with various forms of estrogen or progestin in the populations tested.

In terms of primary prevention trials, WHI was the largest test to date. In this prospective trial, 16,608 postmenopausal women with a mean age of 63 years were randomized to conjugated equine estrogens (0.625 mg daily) plus medroxyprogesterone acetate (2.5 mg daily) in 1 tablet or placebo.4 After 5.2 years of treatment, the absolute risks and benefits of HT in WHI were small in magnitude but in relative terms the HT group had a 29% overall increased risk of CHD (95% CI, 2%-63%), a 41% increased risk of stroke (95% CI, 7%-85%), and a 113% increased risk of pulmonary embolism (95% CI, 39%-225%). As in HERS, the elevation in CHD risk was most apparent during Year 1 (Table 2).4,12 That the duration of HT will impact the observed CHD benefits or risks also is suggested in the decade-long NHS and may reflect the long period (≥5 years) required for “at-risk” plaques to develop from early fatty streaks. In this regard, some have speculated that an overall beneficial effect of treatment would have been seen had the WHI trial been carried out for the originally scheduled 10 years.

The increase in breast cancer risk was of borderline significance at an RR of 1.26 (95% CI, 1.00-1.59) and the risks of colorectal cancer and hip fracture were reduced in the HT group (0.63; 95% CI, 0.43-0.92 and 0.66; 95% CI, 0.45-0.98, respectively). There was no significant difference in total mortality. In the estrogen-only arm of the WHI study (n=10,739), HT did not appear to affect the risk of CHD (RR 0.91; 95% CI, 0.75-1.12) whereas stroke risk was still elevated (RR 1.39; 95% CI, 1.10-1.77), the risk of hip fracture

### Table 1. Rate of Primary Coronary Heart Disease Events* in the Heart and Estrogen/Progesterone Study

<table>
<thead>
<tr>
<th>Period</th>
<th>Estrogen-Progestin Number</th>
<th>Placebo Number</th>
<th>Relative Hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>57</td>
<td>38</td>
<td>1.52 (1.01–2.29)</td>
</tr>
<tr>
<td>Year 2</td>
<td>47</td>
<td>48</td>
<td>1.00 (0.67–1.49)</td>
</tr>
<tr>
<td>Year 3</td>
<td>35</td>
<td>41</td>
<td>0.87 (0.55–1.37)</td>
</tr>
<tr>
<td>Years 4 + 5</td>
<td>33</td>
<td>49</td>
<td>0.67 (0.43–1.04)</td>
</tr>
</tbody>
</table>

*Nonfatal myocardial infarction and coronary heart disease death, per 1000 women-years. CI = confidence interval. Data from Hulley S, et al.4

### Table 2. Rate of Coronary Heart Disease (CHD)* in the Women’s Health Initiative Trial

<table>
<thead>
<tr>
<th>Period</th>
<th>Estrogen-Progestin Number</th>
<th>Placebo Number</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>42</td>
<td>23</td>
<td>1.81 (1.09-3.01)</td>
</tr>
<tr>
<td>Year 2</td>
<td>38</td>
<td>28</td>
<td>1.34 (0.82-2.18)</td>
</tr>
<tr>
<td>Year 3</td>
<td>19</td>
<td>15</td>
<td>1.27 (0.64-2.50)</td>
</tr>
<tr>
<td>Year 4</td>
<td>32</td>
<td>25</td>
<td>1.25 (0.74-2.12)</td>
</tr>
<tr>
<td>Year 5</td>
<td>29</td>
<td>19</td>
<td>1.45 (0.81-2.59)</td>
</tr>
<tr>
<td>Year 6 + later</td>
<td>28</td>
<td>37</td>
<td>0.70 (0.42-1.14)</td>
</tr>
</tbody>
</table>

*Acute myocardial infarction (MI) requiring overnight hospitalization, silent MI, or coronary heart disease death, with number of patients and annualized percentage. CI = confidence interval. Adapted with permission from Manson JE, et al.2
was decreased (RR 0.61; 95% CI, 0.41-0.91), and there were no significant differences in terms of breast cancer, pulmonary embolism, colon cancer, or in global risk of adverse events.  

Clearly, HT does not reverse CHD. The evidence also indicates that HT has a significant prothrombotic effect; this effect is seen mostly among the subgroup of women with genetic thrombotic polymorphisms who were at elevated risk from oral contraceptives and also among those postmenopausal women using oral rather than transdermal HT.  

Given this evidence of increased risk of clinical CVD events with HT in primary or secondary prevention, HT is now reserved for limited duration and low-dose in treating menopausal symptoms. The specific indications may include treatment of sleep disturbances, hot flashes, and vaginal dryness as well as the prevention of postmenopausal osteoporosis.  

As indicated in the absolute values of events, the overall risks and benefits due to HT are small and so those women who do need to take hormones to control their menopausal symptoms can be reassured about low-dose and short-term use. However, because these women generally are younger than those enrolled in the large primary and secondary studies described above, the risk-benefit equation in this younger group remains somewhat unclear. In fact, there is some clinical evidence that unopposed estrogen has an antiatherosclerotic effect in younger postmenopausal women and 2 new studies suggest that women who initiate HT closer to the time of menopause may actually have lower CV risks than women starting HT later in life.  

The first of the new studies is a subgroup analysis from WHI. Based on preliminary suggestions of lower CHD among women who had undergone hysterectomy and were age 50 to 59 when WHI started, researchers revisited the final data from the estrogen-only arm of the study. The cumulative hazard ratio for the primary outcome (MI or coronary death) is clearly lower in adherent participants aged 50 to 59 years (0.61; 95% CI, 0.25-1.50) versus those in the 2 older age groups (0.86 in those aged 60 to 69 years; 95% CI, 0.60-1.25, and 1.10 in those aged 70 to 79 years; 95% CI, 0.69-1.73) (Figure 3). Overall, there were 21 cases of CHD (0.17%) in the younger women taking estrogen versus 34 events (0.27%) in those taking placebo. The researchers conclude that though there is no overall protection against coronary events or deaths in generally healthy postmenopausal women over a 7-year period, there are suggestions of lower coronary risk in younger postmenopausal women. These results suggest that a prospective study should be directed at evaluating the impact of HT on CVD in younger women.  

The second large study examining the relation of CHD to HT according to the timing of hormone ini-
tiation was based on data from the large prospective NHS. This is an ongoing study of 121,700 female nurses who were aged 30 to 55 upon study initiation in 1976. Based on information on hormone use obtained in biennial questionnaires, the researchers concluded that women beginning HT near menopause had a significantly reduced risk of CHD. For estrogen use alone, the RR of major CHD for current users was 0.66 (95% CI, 0.54-0.80) compared with women who never used HT; for combined HT, the RR was 0.72 (95% CI, 0.56-0.92). These results support the possibility that the timing of HT initiation in relation to menopause onset or to age might influence coronary risk, and suggest again that prospective trials of HT in younger women (perimenopause and early postmenopause) is needed.

Although these results are intriguing, the limitations of these 2 studies are clear. In the WHI subgroup analysis, the number of younger women and events were quite small. Conversely, in the NHS as in so many other observational trials, only a small proportion of subjects were started on HT a long time after menopause. Therefore, it must be emphasized again that the best evidence to date still supports use of HT only for short-term relief of vasomotor symptoms and not for long-term use intended to provide disease prevention—at any age.

At least 2 major prospective trials are under way to investigate the potential benefits and risks of early versus late intervention with HT in perimenopausal women. In the Early vs Late Intervention Trial with Estradiol (ELITE), more than 500 postmenopausal women will be randomized to daily 17β estradiol or placebo. They will also receive micronized vaginal progesterone 10 days per month. In the Kronos Early Estrogen Prevention Study (KEEPS), more than 700 postmenopausal women aged 40 to 55 years (no menses >6 months but <3 years) will be randomized to (1) oral conjugated estrogen and placebo skin patch, or (2) oral placebo and transdermal estradiol skin patch, or (3) double placebo. They will also receive oral micronized progesterone, 200 mg/day for 12 days each month. In both ELITE and KEEPS, imaging of the carotid artery will provide a key outcome.

CONCLUSION

In summary, previous studies often incorrectly measured menopause and preliminary evidence suggests that estrogen deficiency may be a potent risk factor for angiographic CAD in young premenopausal women and, further, that HT may be beneficial in perimenopausal women. However, prospective studies are needed to validate these findings, to determine cause and effect relationships, and to clarify the practical clinical implications. These studies should benefit from use of more accurate algorithms to classify exact menopausal status. These new prospective studies also must pay close attention to both age at initiation and duration of therapy as factors impacting HT benefits and risks. The role of cholesterol levels, inflammatory biomarkers, and statin therapy are other areas worthy of analysis in ongoing HT research. Until these studies are complete, HT must be limited to short-term and low-dose use in women who require assistance in managing the symptoms of menopause.

Prior to undergoing peer review, this article was developed with the assistance of a staff medical writer. The author had final approval of the article and all its contents.

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