Editorial

Postmenopausal Hormone Therapy
A Reversal of Fortune

Karin B. Michels, ScD, MSc; JoAnn E. Manson, MD, DrPH

How did it become common clinical practice in past decades to prescribe postmenopausal hormones for the prevention of coronary heart disease (CHD)? Postmenopausal hormone therapy (HT), although approved by the US Food and Drug Administration for the treatment of postmenopausal symptoms and the prevention of osteoporosis, was never approved for the prevention of CHD. The recent data from the Women’s Health Initiative (WHI) and other randomized clinical trials (RCTs) indicate that combined estrogen and progestin may increase, rather than decrease, CHD risk.1 This news has alarmed women worldwide and has left physicians uncertain what to recommend to their patients. Recently, the North American Menopause Society released recommendations stating that estrogen and progestin should not be prescribed for primary or secondary prevention of CHD.2 The effect of unopposed estrogen and other formulations of HT on CHD remains unclear; more insight on the former will emerge from the still-ongoing estrogen component of the WHI.

The surging popularity of HT use during the past few decades was largely based on findings from observational epidemiologic studies.3-4 Observational studies suggested that HT may reduce the incidence of CHD, fractures, and colorectal cancer but may increase the incidence of endometrial cancer, breast cancer, stroke, and venous thromboembolism.4,5 Notably, except for the divergent findings about CHD, the WHI findings were largely concordant with the observational studies (Figure). The relative risks for hip fractures and colorectal cancer with HT were reduced, whereas those for breast cancer, venous thromboembolism, and stroke were increased. At surprising odds with the observational studies, the WHI found a 29% increase in CHD after an average of 5.2 years of follow-up.1 Before the WHI, other RCTs had already begun to cast doubt on the cardiovascular benefit of HT. The Heart and Estrogen/progestin Replacement Study (HERS) had reported an overall null result and an increased risk of CHD in the first year among women with prior heart disease who were randomized to HT.6 Consequently, the American Heart Association recommended in 2001 not to initiate HT for secondary prevention of CVD.7

What factors account for the widely divergent findings on HT and CHD from observational studies and RCTs? This question is particularly relevant for cardiovascular specialists because the answers could lead to important new insights about the pathogenesis of atherothrombotic events and could inform future research in this area. A cardioprotective effect of estrogen itself is still uncertain. Several physiological effects of exogenous estrogen are consistent with cardioprotection: Estrogen reduces LDL and increases HDL levels; reduces Lp(a) lipoprotein, fibrinogen, plasminogen-activator inhibitor type 1, and insulin levels; inhibits oxidation of LDL; and improves endothelial vascular function.8 Estrogen therapy, however, has adverse physiological effects, including increasing triglycerides and C-reactive protein and promoting thrombosis. Adding a progestin attenuates some of the lipid benefits, particularly the HDL increase, but it does not seem to counter the prothrombotic effects of estrogen.8

Currently, clinical data on HT and CHD are available from more than 40 observational studies and from 7 RCTs (5 RCTs on secondary prevention9-13 and 2 RCTs on primary prevention1,14; Table). A meta-analysis of 40 observational studies suggested a 50% reduction in the risk of CHD associated with current estrogen use.3 Most of these studies include women who used unopposed estrogen; limited data are available from observational studies on estrogen and progestin supplementation.

The first secondary prevention trial, HERS, did not find any cardiovascular benefit of estrogen-progestin supplementation (Table).9 Subsequent trials have found either no cardioprotection or an increased risk of CHD events with HT (Table).10-13 Most of these trials tested oral conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), but the results with transdermal 17β-estradiol with and without norethindrone11 and estradiol valerate13 were similar (Table). Primary prevention RCTs including clinical CHD end points have been sparse and have also suggested an excess risk.1,14

Why then do the results from the observational studies and the RCTs on the association between HT and CHD seem to send different messages? There are several possible explanations, both methodologically and biologically based. Methodological explanations focus on the observation that long-term HT users in epidemiologic studies differ in many ways from nonusers. Women on HT in observational studies are more health conscious, thinner, and more physically active, and they have a higher socioeconomic status and better access to health care than women who are....
not on HT. Self-selection of women into the HT user group could generate uncontrollable confounding and lead to “healthy-user bias” in observational studies. Moreover, individuals who adhere to medication have been found to be healthier than those who do not, which could produce a “compliance bias.” The question remains, however, of why the observational studies and RCTs are concordant for stroke, venous thromboembolism, fracture, and cancer, all of which have lifestyle determinants. In particular, CHD and stroke have similar risk factor profiles. Thus, it is unlikely that the healthy-user bias or the compliance bias in observational studies fully explains the differences.

### Results of RCTs of Postmenopausal HT and CHD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Group</th>
<th>Age Range at Entry (Mean), y</th>
<th>Treatment</th>
<th>Mean Duration, y</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart and Estrogen/progestin Replacement Study⁹</td>
<td>2763 women with documented CHD</td>
<td>44–79 (66.7)</td>
<td>0.625 mg of oral CEE plus 2.5 mg of MPA or placebo</td>
<td>6.8</td>
<td>Primary CHD events: RR=0.97 (95% CI 0.82–1.14)</td>
</tr>
<tr>
<td>Estrogen Replacement and Atherosclerosis Trial¹⁰</td>
<td>309 women with CHD</td>
<td>42–80 (65.8)</td>
<td>0.625 mg of oral CEE, 0.625 mg of oral CEE plus 2.5 mg of MPA, or placebo</td>
<td>3.2</td>
<td>No significant differences in rates angiographic stenoses or clinical events</td>
</tr>
<tr>
<td>Papworth HRT Atherosclerosis Study¹¹</td>
<td>255 women with CHD</td>
<td>55+ (66.5)</td>
<td>Transdermal 17β-estradiol alone or with cyclic norethindrone, or placebo</td>
<td>2.6</td>
<td>CHD events: RR=1.49 (95% CI 0.93–2.36)</td>
</tr>
<tr>
<td>Women’s Angiographic Vitamin and Estrogen Trial¹²</td>
<td>423 women with CHD</td>
<td>Mean: 65</td>
<td>0.625 mg of oral CEE plus 2.5 mg of MPA, or placebo</td>
<td>2.8</td>
<td>Slightly greater angiographic progression with HT than placebo; CVD events: HR=1.9 (95% CI 0.97–3.6)</td>
</tr>
<tr>
<td>Estrogen in the Prevention of Reinfarction Trial¹³</td>
<td>1017 women with CHD</td>
<td>50–69 (62.6)</td>
<td>2 mg estradiol valerate or placebo</td>
<td>2</td>
<td>CHD events: RR=0.99 (95% CI 0.70–1.41) All-cause mortality: RR=0.79 (95% CI 0.50–1.27)</td>
</tr>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
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<tr>
<td>Overview of 22 HT trials¹⁴</td>
<td>4124 women enrolled in RCTs of HT</td>
<td>Not provided</td>
<td>Several formulations of HT or placebo or other therapy</td>
<td>&lt;3</td>
<td>CVD events: RR=1.39 (95% CI 0.48–3.95)</td>
</tr>
<tr>
<td>Women’s Health Initiative¹</td>
<td>16 608 women at usual risk of CHD</td>
<td>50–79 (63)</td>
<td>0.625 mg of oral CEE plus 2.5 mg of MPA, or placebo</td>
<td>5.2</td>
<td>CHD events: HR=1.29 (95% CI 1.02–1.63)</td>
</tr>
</tbody>
</table>

CEE indicates conjugated equine estrogen; MPA, medroxyprogesterone acetate.
Although it is possible that the end point of CHD is particularly susceptible to these biases.

Another methodological issue to consider is the potential failure of observational studies to capture early clinical events that occur within a year or two of initiation of HT. In epidemiologic studies, information on HT use may not be updated, or it may be infrequently updated during follow-up. If a clinical event follows soon after HT initiation, it could be wrongly classified as occurring during a “nonuse” interval. This issue could be more important for CHD than for other end points because RCTs have indicated an early and short-term excess risk of CHD events but delayed and/or more persistent elevated risks of stroke, deep vein thrombosis, and breast cancer.

In addition, several biological factors could contribute to the differences between observational studies and RCTs. WHI participants differed in a number of ways from women taking HT in observational studies. In an observational setting, free-living women are studied, who make the decision together with their physicians whether to take HT, generally on reaching menopause. One important criterion for this decision is the presence of menopausal symptoms; women who have menopausal symptoms are more likely to request HT. Women with such symptoms may be those who have the lowest endogenous estrogen levels and therefore may have the greatest benefit from exogenous estrogen supplementation.

Furthermore, although women in the observational studies generally initiated HT use at onset of menopause, most of the participants in the WHI started HT many years after menopause. In fact, 67% of women in WHI were age 60 years or older.1 It is conceivable that many of these older women already had subclinical CHD. The prothrombotic effect of estrogens may manifest itself predominantly among women who initiate HT well into their menopause, whereas women who start HT early after the onset of menopause may experience cardiovascular benefit from estrogens. This possibility derives support from nonhuman primate data.16 However, women in the WHI who initiated HT at 50 to 59 years of age did not have lower hazard ratios for CHD than older women.17 Moreover, women with prior CHD in the WHI assigned to HT had the same hazard ratio for CHD as women without prevalent CHD.1 These data suggest that differences by age at initiation of HT and underlying stage of atherosclerosis may not be sufficient explanations for the observed differences between epidemiologic studies and RCTs. Another consideration is that WHI participants had higher body mass than women in observational studies.5 Potential modification of the HT–CHD relation by body mass index, which correlates inversely with endogenous estrogen levels, is important to explore; such analyses are in progress.

Another possible explanation for the differences between epidemiologic studies and RCTs that has been suggested is the inclusion of silent myocardial infarctions as end points in the WHI. While observational studies generally do not capture this end point, less than 5% of the major CHD events in the WHI were silent myocardial infarctions; moreover, exclusion of silent myocardial infarctions did not appreciably alter the findings.1 Therefore, this could not be a plausible explanation for the differences observed.

Differences in the formulations and doses of HT may also have contributed to the divergent findings from observational studies and RCTs. As previously mentioned, most women in observational studies used unopposed estrogen. Although HERS and the WHI provide important data on continuous-combined oral CEEs (0.625 mg/d) and MPA (2.5 mg/d), the results cannot be generalized to unopposed estrogen, sequential progestin use, or other formulations of estrogens and progestins, other dosages, or other routes of administration. Future research on other regimens is needed. Identifying biomarkers and genetic factors that predispose to adverse effects of HT may make it possible to target HT therapy more appropriately.

In conclusion, several methodological and biological factors may have contributed to the divergent findings from observational studies and RCTs. Clearly, more research is needed to elucidate the relative importance of each of these factors. In the meantime, a role remains for combined estrogen and progestin supplementation in the treatment of severe menopausal symptoms. Such therapy, however, should involve the lowest effective dose and the shortest duration of treatment to relieve symptoms.2 HT should not be initiated or continued for primary or secondary prevention of cardiovascular disease.

References


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