Is the WHI Relevant to HRT Started in the Perimenopause?

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The Women's Health Initiative (WHI) hormone replacement therapy (HRT) estrogen plus progestin (E+P) and estrogen-only arms are part of a large NIH-sponsored randomized controlled trial (RCT). Both arms were terminated prematurely after 5 and 8 yr, respectively. The E+P arm showed non-statistically significant increased incidences of cardiovascular events and breast cancer, whereas the E-only arm did not. Both arms showed an increased rate of thromboembolic events and stroke. Both arms showed protection against fractures and with protection against colon cancer only in the E+P arm. These results have been widely generalized as indicating a negative risk/benefit ratio for HRT in menopausal women.

The WHI results are at odds with results of large epidemiological studies that showed protection against cardiovascular disease. Although the latter data are, in part, confounded by a "healthy user bias," much of the inconsistency may be explained by the fact that women in the latter studies initiated HRT at the menopausal transition, whereas the WHI trial was conducted in older women (mean age 63.3), who were, on average, approx 12 yr postmenopausal. In addition, older trials included women on either unopposed estrogen therapy (ERT) or cyclic HRT regimens.

Whatever other forces may have been at work, observational and experimental evidence supports the conclusion that estrogen's atheropreventive effects predominate early, in the absence of vulnerable plaque to be ruptured or thrombotic episodes propagated by narrowed lumens and intravascular turbulence. On the contrary, age-related adverse effects of HRT may prevail once complex atheromas and luminal narrowing/irregularity are established. It is known that prevalence of subclinical "at-risk" atherosclerotic lesions increases in women during the first 5–10 yr after menopause. Furthermore, animal and clinical evidence supports the use of lower doses of estrogen than were employed in the WHI in older/longer postmenopausal women.

Therefore, we suggest that conclusions from the WHI should be strictly limited to the WHI Writing Group's own published interpretation that initiation of daily continuous treatment with combined oral conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) or 0.625 mg conjugated equine estrogen, alone, in older postmenopausal women is inadvisable for prevention of heart disease. Other conclusions on the use of such regimens are moot, since they are not appropriate clinical treatments. The allowance of "age creep" to generalize these conclusions to subjects not studied in adequate power by the WHI is neither scientifically correct nor appropriate for the development of clinical practice guidelines.

Because of the limitations on the interpretation of the WHI, new RCTs are needed to resolve these questions. These RCTs should be designed to resolve whether estrogen treatment started during the menopausal transition is cardioprotective. Meanwhile, decisions of whether to initiate HRT for peri-menopausal women or to maintain it in women on long-term HRT started for estrogen-deficiency symptoms in the perimenopause should continue to be individualized based on consideration of all available data.

Key Words: Menopause; hormones; cardioprotection; RCT.

Introduction

It is the authors' contention that, because investigations were mostly carried out on women who were more than a decade postmenopausal, data from the Women's Health Initiative (WHI) hormone replacement therapy (HRT) study *(1)* do not address the risks and benefits of HRT initiated in women during the menopausal transition. We believe that considerations discussed below make a case that the recently

published WHI results have been overgeneralized by both health professionals and the lay media, and that the abandonment of HRT by many peri- and post-menopausal women is not supported by currently available data.

Background

Observational Trials on HRT and Cardiovascular Protection

Before the publication of the Heart and Estrogen/Progestin Replacement Study (HERS) trial *(2)* in 1998, a large body of evidence supported the hypothesis that the balance between risks and benefits of long-term HRT was favorable for most women, though questions remained regarding optimal dosing, timing, duration, molecular structure, and route of administration of these agents. Epidemiologic data, derived from large, carefully conducted cohort, retrospective and prospective studies, demonstrated that, while long-term HRT was associated with a small increase in breast cancer risk *(3,4)*, in some *(5–8)*, but not all *(9,10)*, studies there appeared to be clinically relevant (30–50% reductions) protection against coronary heart disease and all-cause mortality *(11–15)*, as well as osteoporotic fractures *(16–18)*. Lending strength to the concept of heart and bone protection was a body of basic investigations demonstrating a variety of credible physiological mechanisms by which estrogen improves risk factors for atherosclerosis and acts on bone to reduce calcium loss. The favorable risk/benefit estimates owed largely to the fact that atherosclerotic heart disease is approximately five times more likely to kill women over age 60 than is breast cancer and that osteoporotic hip fractures contribute about as much to morbidity and mortality as does breast cancer in women over 70 *(6)*.

Need for Randomized Clinical Trials

Circumspection in application of the information from observational studies seemed appropriate, because of the lack of randomized controlled trials (RCTs) while in one pioneering RCT, there was no difference in cardiac event rate in 84 women randomized to estrogen + progestin or placebo after 10 yr *(19)*. However, there have been RCT data examining the effects of HRT on intermediate or surrogate endpoints that did support the notion that HRT may be cardioprotective. For example, in one prospective study, using progression of carotid intimal–medial thickness as a surrogate for coronary disease, observations in 86 women showed increases in the placebo group and regression among HRT users, which difference appeared to be independent of lipoprotein concentrations *(20)*. Another relatively recent trial also showed average rate of progression of carotid intimal medial thickness to be significantly lower in estradiol-than in placebo-treated healthy postmenopausal women not receiving lipid-lowering drugs *(21)*. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial compared conjugated equine estrogen (CEE) with three different CEE–progestin combinations and placebo in 875 healthy postmenopausal women aged 45–64 yr *(22)*. In each of the groups of women receiving CEE-containing regimens, there were improvements in HDL and LDL cholesterol, and fibrinogen, with worsening of triglycerides, and no effects on blood pressure or glucose tolerance. However, the PEPI trial was neither long enough nor large enough to demonstrate differences in clinical cardiovascular endpoints.

Because, there were no RCTs of sufficient power with clinical event endpoints to confirm or refute the cardioprotective benefits suggested by available studies *(23)*, the FDA concluded that the level of evidence was insufficient to approve an HRT regimen for cardiovascular disease prevention. It was also noted that the findings of the observational and epidemiologic studies were weakened somewhat because the demographics of HRT users and non-users in many of these studies differed in important ways. In particular, women choosing to take HRT tended to be better educated and to have higher income levels than non-users, both factors associated, *a priori,* with reduced risk of coronary events, and which might therefore confound results of observational studies *(15)*. Thus, there was clearly a need for RCTs to address this issue.

Treatment or Secondary Prevention RCTs with Clinical End Points

The HERS trial *(2)* published in 1998, was a study of outcomes of starting HRT treatment in women with recent myocardial infarction and other known coronary disease, who were thus at increased risk for future cardiac events. HERS demonstrated no effect of HRT on cardiovascular outcomes over the entire duration of the study. In fact, worse outcomes occurred in women in the early portion of the trial. Consistent with these findings, carotid intimal–medial thickness (IMT) measurements from a subset of patients in the HERS trial *(24)* showed no significant difference between the rates of progression in the hormone group and the placebo group (26 vs 31 µm/yr; *p* = 0.44). Similarly, findings from an independent study employing serial quantitative coronary angiography demonstrated that established coronary narrowing progressed at equal rates after starting CEE or placebo treatment *(25)*. In summary, these treatment or secondary prevention studies demonstrated a lack of cardiovascular benefit of beginning HRT in women several years beyond the menopause with symptomatic cardiovascular disease. They did not address the question of whether HRT reduces cardiovascular risk in women without established atherosclerosis, the population most relevant to the clinically typical initiation of HRT.

The recently published results from the placebo and estrogen/progestin arms of the WHI HRT study (which latter was discontinued after 5–6 yr by the Data Safety Monitoring Board), have raised the most serious doubts to date regarding the ability of HRT to reduce cardiovascular risk. The study arms reported on comprised two groups, totaling

approx 16,000 women, and compared the combination of 0.625 mg of CEE and 2.5 mg of medroxyprogesterone acetate (MPA) (Prempro®, Wyeth), with placebo. A "final" analysis of the cardiovascular data *(26)* reported an excess (39 vs 33 per 10,000 patient years) of cardiovascular events in the HRT group, despite significant favorable effects of HRT on total, LDL, and HDL cholesterol, glucose, and insulin. Results, published in the *Journal of the American Medical Association* in July 2002 *(1)*, showed HRT to be associated with more strokes (29 vs 21 per 10,000 patient years), and thromboembolic disease (34 vs 16 per 10,000 patient years) and also found the HRT group to have significant increases in incidence of breast cancer (38 vs 30 per 10,000 patient years). There was no difference in deaths (52 vs 53 per 10,000 patient years) *(1)*. With the exception of venous thrombosis, confidence intervals for recorded adverse effects were barely statistically significant and were non-significant after adjustment. Beneficial effects included reductions in the rates of colon cancer (45 vs 67), and femoral fractures (147 vs 191), which were considered insufficient to counterbalance the occurrence of adverse effects. Other WHI studies reporting no positive effects of HRT on quality of life *(27)* or mild cognitive insufficiency and dementia *(28,29)* were also published. Although overall mortality was equal in both groups, the investigators in the WHI study concluded that HRT was not beneficial overall in postmenopausal women, based mainly on the excess of breast cancer and the failure to protect against cardiovascular disease. Given the above interpretation of the WHI E+P study outcome, millions of women are now questioning whether they ought to avoid initiation of HRT for perimenopausal symptoms, or should discontinue HRT, after many years of use.

RCT Results vs the Observational Studies

Why are the results of this randomized placebo-controlled trial for cardiovascular disease so different from observations over 30 yr of epidemiologic studies? It is conceivable that there were confounding baseline differences between HRT users and non-users in the observational trials so pronounced that they could have accounted for the observed lower risk of heart disease in HRT users. However, various attempts to match subpopulations or control statistically for known confounds, such as income, education, and so on, have shown persistent cardiovascular protection by HRT in most cases *(5,13,15,30)*. In contrast, no HRT-related protection against cardiovascular disease was found after correction for socioeconomic factors in a recent large meta-analysis of previous population studies *(31)*.

Might factors other than "healthy user bias" explain the discrepancy between the WHI trial and the previous observational population studies? A key observation, pointed out by Lemay *(32)*, is that the older age distribution and relatively late start of HRT in the WHI study does not correspond to the traditional use of HRT. The observational studies were overwhelmingly studies of women in whom ERT or HRT was started in the peri-menopause (ages 45–55) for symptoms of estrogen deficiency (such as hot flashes, insomnia, mood swings, and dyspareunia). Unlike these prior studies, the WHI enrolled predominantly older women (mean age 63.3), who were free of significant menopausal symptoms.

Design of the WHI

The decision to study older women in the WHI was based on the plausible assumption that HRT would be atheropreventive regardless of when it was started. Indeed, at the time, some clinicians were employing this assumption in clinical practice and were starting some women on HRT for the first time many years into the menopause. Given this assumption, it appeared simpler and better to study symptom-free older postmenopausal women, rather than younger, symptomatic, perimenopausal women for several reasons:

1. One could insist on a minimum of one full year without menses as a study entry criterion, conveniently and definitively characterizing subjects to be in the postmenopausal state.
2. Older women would have a risk of future CHD events far higher than younger perimenopausal women, thus a smaller sample size would suffice.
3. Women across a broad range of years postmenopause would be more plentiful than early perimenopausal women, facilitating subject recruitment.
4. It was anticipated that a positive study result would be more broadly applicable and would suggest that millions of women who had never taken HRT (or who had stopped it years earlier) could begin (or begin again) to receive its anticipated atheropreventive benefits.
5. Exclusion of subjects with estrogen deficiency symptoms would enhance subject blinding and compliance with placebo because symptomatic perimenopausal women receiving placebo might drop out more frequently than the treated women.

We contend that the assumption that estrogen would reduce CHD, irrespective of the timing of its initiation, combined with the aforementioned advantages of studying later-onset HRT, "derailed" the intent of WHI to study the estrogen-cardioprotection hypothesis.

To test this contention, we performed a power analysis using the WHI-reported number of women in the trial's estrogen plus progestin arm who were 50–54 yr of age and moderately to severely symptomatic, to test whether the WHI could have discerned a threefold difference in the number of cardiovascular events between the placebo controls and the hormone-treatment women. This age range was used, because the observational trials that showed cardioprotective effect of HRT were based on women who were in the menopausal transition at the time that they began HRT. The power analysis indicates that the WHI was 10-fold underpowered to identify a threefold difference between groups *(33)*.
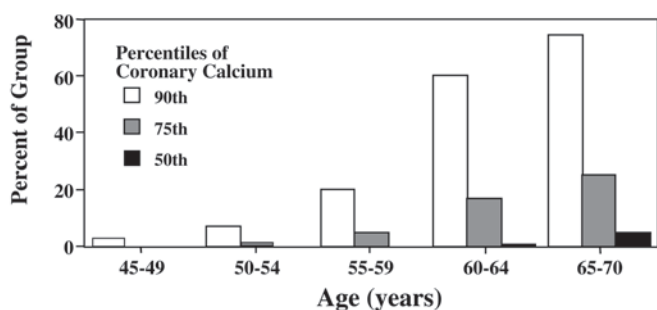
Fig. 1. Distribution profile for atherosclerotic plaque burden as measured by coronary calcium percentile in asymptomatic women undergoing electron beam tomography [data plotted from Raggi et al. *Circulation* **10,** 850–855, 2000].

Fig. 2. Rates of coronary heart disease outcomes and absolute numbers of events (numerals in bars) by year in the E+P and Placebo groups in the WHI randomized controlled hormone trial [data plotted from *JAMA* **288,** 321–333, 2002].

Another feature of the study population deserving consideration is the significant numbers of subjects who smoked or who were obese, hypertensive, or diabetic, and even some women with a prior history of thromboembolic disease (generally considered a contraindication for HRT). The relationships of these factors to relevant outcomes have not yet been published, but the inclusion of patients more susceptible to harmful effects of HRT than those in the prior studies could have contributed to the adverse results. For example, in the CSPII trial *(34)*, in 300,000 postmenopausal women followed for >12 yr, relative risks for coronary heart disease incidence in HRT users vs non-users were 0.49, 0.77, 0.70, and 0.95, and of death from coronary heart disease were 0.49, 0.72, 0.77, and 1.45 in women whose BMIs were, respectively, <22, 22–<25, 25–<30, and ≥30 kg/m^2. Thus the fact that 34% of WHI women had BMIs > 30 kg/m^2 may have decreased the likelihood of finding a cardioprotective effect of treatment.

Perhaps most important is the question whether women in the WHI trial may have already had a greater prevalence of atherosclerosis before HRT initiation than did women in the observational studies. This is critical because the HERS study *(2)*, as noted above, demonstrated a lack of cardiovascular benefit in women with established coronary artery disease. Figure 1 shows the distribution profile for atherosclerotic plaque burden in over 4000 asymptomatic women estimated by coronary calcium percentile as determined from electron beam tomography *(35)*. It is evident that the great majority of women at the age of the menopausal transition *(45–55)* have little or no plaque burden, whereas calcified plaque (and presumably total plaque burden) increases rapidly after the menopause. Because the WHI study randomized women ages 50–79, with only 33% between the ages of 50 and 59, producing a mean age of 63 yr, it is likely that many of these women, although asymptomatic, had significant atherosclerosis. That estrogen may help prevent progression of atheromas from simple to complex is suggested by a recent study in 2213 postmenopausal women of
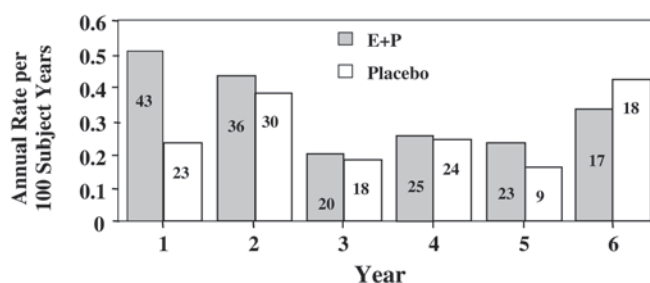
whom 53% were current users of MHT, in which MHT users were significantly more likely to have a coronary artery calcium score <100 and less likely to have a score >400 than non-users, after adjustment for cardiac risk factors *(36)*.

Possible Mechanisms for WHI Adverse Results

As in the HERS trial *(2)*, most of the excess cardiovascular events in the HRT vs the placebo group occurred in the first (and possibly the second) year (Fig. 2). How could estrogen treatment have increased cardiovascular event rates so quickly, given that atherosclerotic plaque normally accumulates and evolves relatively slowly? The likely explanation is that HRT effects precipitated acute events at pre-existing plaques, rather than accelerated the atherosclerotic process itself. There are a number of potential mechanisms for such effects. One possibility is that oral estrogens, acting via a "first-pass" effect on the liver, increase the tendency of blood to clot by increasing clotting factors and decreasing anticlotting factors *(37–39)*. This effect could also help account for the excess of other thrombotic disease observed in the HRT group. The latter supposition is given further support by a recent publication *(40)* in which an excess risk of venous thromboembolism was observed in women receiving oral, but not transdermal, estrogens. A recent study *(41)* showing that oral, but not transdermal, estrogens, elevated C-reactive protein (CRP), an inflammatory factor correlated with increased cardiovascular disease risk *(42–44)*. Thus, "first-pass" effects with negligible influence in women with little or no pre-existing atherosclerosis, could have substantial effects on early event rates in women with vulnerable plaque.

In addition to the above, age may play a role. Trials were conducted using the same oral estrogen plus progestin as used in the WHI, to assess its ability to decrease menopausal hot flushes. In the two trials that were reviewed there was no differences in venous thromboembolism. In fact, far fewer events were seen than in the WHI populations *(80)*.
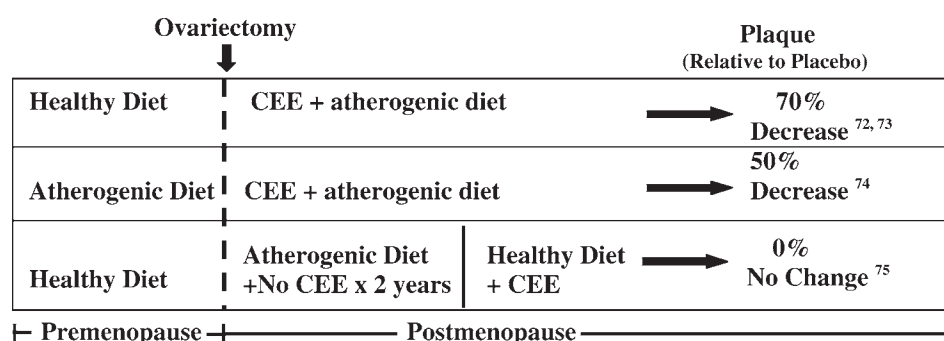
Fig. 3. Influence of timing of initiating estrogen treatment on the effect/lack of effect on coronary artery atherogenesis in cynomolgus monkeys. (Composite figure drawn from refs. *72–75*).

The same mechanisms affecting coagulation and inflammation that we hypothesize may have contributed to the higher rates of cardiovascular events, could also have contributed to the higher rates of stroke and loss of cognitive function observed in the WHI study. A recently published more complete analysis of the WHI stroke endpoint *(45)* revealed that 79.8% of strokes were ischemic. The adjusted hazard ratio (HR) for HRT vs placebo was significant for ischemic (HR=1.44; 95% CI, 1.09–1.90) but not for hemorrhagic or combined strokes, suggesting an etiologic role for hypercoagulability. However, higher levels of inflammation-associated factors (C-reactive protein, IL-6, E-selectin) appeared to be more predictive of stroke risk than those related to clotting (fibrinogen, Factor VIII).

Also bearing on the question of early vs late atheroprotection is a body of experimental evidence suggesting that the effects of estrogen on atherosclerosis are divergent depending on when therapy is started *(46)*. This evidence comes from two lines of research. First, basic studies indicate that there are several distinct effects of estrogen on mechanisms of atherosclerosis, some of which would be predicted to be favorable and others adverse. The probable anti-atherogenic effects of estrogens include:

1. Favorable effects on arterial wall function such as arterial compliance *(47–49)*, blood pressure lowering *(50–52)*.
2. Antioxidant effects *(53–56)*.
3. Favorable lipid effects including lowering of LDL-C and Lp(a) and raising of HDL-C levels *(22,57,58)*.
4. Favorable effects on certain inflammatory factors, including E-selectin, ICAM-1, and VCAM-1 *(59–61)*, which factors abet infiltration of monocytes into evolving plaque.

Many of the local atheroprotective effects of estrogen may be attenuated by a reduction of arterial estrogen receptors that occurs both with atherosclerosis and aging, possibly due to methylation of the estrogen receptor *(62,63)*. Furthermore, once atherosclerosis has progressed to the stage of the "vulnerable" plaque, protective effects of estrogens may be overbalanced by their negative effects, predisposing to plaque rupture and atherothrombosis. Some of these are:

1. Increased activity of matrix metalloproteinases (MMP2 and MMP9) *(64,65)*.
2. Increased C reactive protein (CRP) *(66–68)*.
3. First-pass hepatic effects increasing coagulation factors (discussed above).

The action of matrix metalloproteinases is believed to contribute to rupture of the fibrous cap of the late-stage atherosclerotic plaque. When such rupture induces formation of a thrombus large enough to reduce or occlude arterial blood flow, an acute coronary event or stroke ensues. Interestingly, there is evidence that not all plaque ruptures result in arterial thrombi large enough to produce infarction, but, depending on a variety of factors, including platelet activation and thrombus propagation, may result in unstable angina, or infarction, or may be clinically silent *(69–71)*. This implies that a pro-thrombotic milieu may make clinical atherosclerotic events more likely (see above). As noted above, an increase in cardiovascular events was seen in the first year of HRT both in HERS and WHI, but only in those not using statins *(72)*, implying that activation of metalloproteinases and other tissue factors is an important component of this phenomenon.

Another body of evidence suggesting that atheroprotective effects of estrogen are limited to the early stages of atherogenesis comes from experiments in surgically postmenopausal female cynomolgus monkeys (see Fig. 3). These studies have shown that treatment of primates fed an atherogenic diet, with CEE, or CEE and MPA, reduced coronary atherosclerosis by as much as 50–70%, if treatment was begun immediately after ovariectomy *(73–75)*. However, no beneficial effect was seen when CEE treatment was delayed for 2 yr *(76)*, leading the investigators to conclude that, in the delayed treatment model, "Hormone replacement therapy did not enhance regression of established coronary atherosclerosis." The finding in an ApoE-deficient mouse model
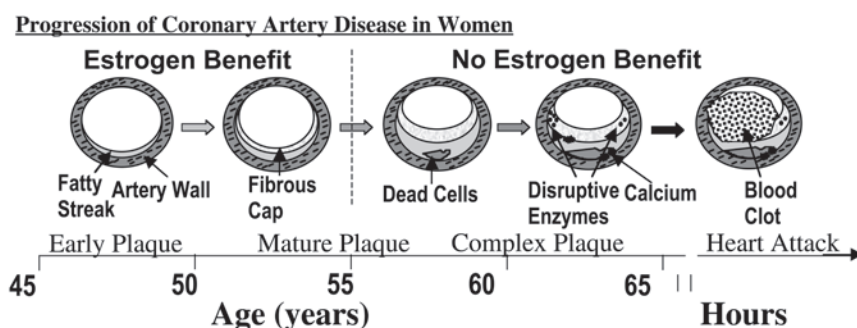
Fig. 4. Progression of atherosclerosis from simple fatty streak to complex "at risk" plaque, requiring several years during the early phase of which estrogen intervention may be preventive, and further progression of complex plaque to rupture with thrombosis and obstruction, requiring hours, and for which process estrogen effects may be adverse.

of atherosclerosis that estrogen inhibits the initiation of fatty streaks but does not inhibit plaque hemorrhage or the progression of established lesions (77) further supports this concept.

Further Considerations Regarding WHI Results and Their Interpretation

Given the data reviewed above, it is a plausible hypothesis that effective inhibition of atherosclerosis by estrogen requires institution of HRT at, or shortly after, the onset of estrogen deprivation. A recently published detailed analysis of WHI HRT data (26) attempted to address the issue of the early initiation of HRT by reporting a similar absence of cardioprotection in women 50–59, 60–69, and 70–79 yr old (risk ratios of, respectively, 1.24, 1.05, and 1.44). However, another WHI publication (27) shows in Table 4 that no more than 287 of the women in each treatment group were moderately to severely symptomatic and 50–54 yr old at randomization. The age-specific incidence of cardiac events for women 50–54 yr of age in the Nurses Health Study was approx 53 per 100,000/year from 1992–1994 (78). For 275 women, this translates to 0.73 expected events over a 5 yr period, so, even if one group had total protection (i.e., no events) and the other had twice the expected rate (as was seen in year one of the WHI study), there would only have been 1.5 vs 0 events during 5 yr of study. Thus, there were clearly insufficient numbers of perimenopausal women to allow conclusions to be drawn regarding this population (33). It seems likely that elapsed time post-menopause would be a more useful measure of risk than age *per se*. The most recent publication on cardiac events in the WHI HRT E+P arm (26) reported risk ratios (HRT vs placebo group) of 0.89, 1.22, and 1.71 for women randomized at menopausal durations of, respectively, <10 yr, 10–19 yr, and 20 yr or more. Although this apparent trend was reported to be non-significant, it is of note that the women with the shortest menopausal duration had a risk ratio less than 1.0, a finding consistent with our central contention.

With regard to the question of later discontinuation of HRT begun for symptoms in the menopause, only 6% of WHI subjects were taking HRT upon presentation for the study, and all of these were required to undergo a 3-mo washout before randomization. Thus, approx 510 and 486 WHI subjects continued and discontinued HRT, respectively, at the beginning of the study. Data on these women have not been presented separately, but it is unlikely that the WHI results will constitute an adequate basis on which to draw the conclusion that HRT, initiated early, should or should not be continued long-term after the menopause.

Most recently, the estrogen only (E-only) arm of the WHI hormone trial was discontinued because there was an excess of strokes in the absence of evidence of reduced risk of heart disease. A preliminary publication of key results (79) reported that, in contrast to the E+P arm, the previously observed trend for an excess of heart disease in the first year was not seen, nor was there an excess of breast cancer. The absence of excess breast cancer risk in the E-alone arm is encouraging in that it suggests that the use of alternate, lower dose, and/or cyclic progestin, rather than constant MPA may ameliorate this adverse effect. As would be expected if the "atherosclerosis window of opportunity" hypothesis is correct, younger women (ages 50–59) in the estrogen-alone arm had an approx 50% reduction in cardiac events (which just missed statistical significance) and, reassuringly, no increase in stroke risk. A quantitatively similar trend for decrease in CHD was also seen in women of all ages in yr 6–8. This latter finding is consistent with the observations of long term protection with as much as 10–15 yr of HRT use in the observational studies and suggests that more than 5 yr of treatment may be needed before effects of estrogen to prevent CVD events can be detected (see Fig. 4).

Summary

Based on the plausible mechanisms and other data described above, it is our contention that the WHI investigators may have looked for a cardioprotective effect of estrogen in women who were too distant from the menopause for such an effect to be detected and that women were not followed long enough for clinical prevention to become evident.

Therefore, although the WHI study has been presented by some as the definitive word on menopausal HRT, it leaves many issues still in doubt. These include:

1. Whether initiating HRT in younger women in, or shortly after, the menopausal transition might provide significant protection against coronary disease.
2. Whether transdermal estrogens, with lesser effects on blood coagulability, C-reactive protein, etc., might have a better risk/benefit profile for coronary heart disease, strokes, or deep vein thrombosis and pulmonary embolism in older women.
3. Whether screening and randomization for estrogen-sensitive clotting mutations, and randomization for risk factors and therapies known to impact atherothrombosis, might identify women at higher as well as lower risk of thrombotic cardiovascular events.
4. Whether use of a different form of progestin, such as micronized or transdermal progesterone, or a 19-nortestosterone derivative (e.g., norethindrone), the intermittent, as opposed to constant, administration, of the progestin, or local delivery of progestin to the endometrium, might result in a lower risk of breast cancer than that observed for oral, constant, MPA. We believe that these and other issues, such as the effect of halting HRT in women taking it since the menopause, cannot be usefully addressed by further analysis of the available data from the WHI.

Therefore, we recommend:

1. A large observational trial be initiated forthwith to document the long-term clinical outcomes in women who initiated HRT or ERT at the menopause comparing those who recently continued vs those who discontinued therapy.
2. New studies be initiated to examine mechanisms of action of estrogens, selective estrogen receptor modulators (SERMs), and various progestins on the process of atherosclerosis at various points in its progression.
3. Small to medium-sized controlled prospective trials of alternative HRT modalities, employing surrogate clinical endpoints for coronary heart disease in perimenopausal women be undertaken to provide evidence as to whether a new large clinical trial of early HRT intervention may be justified, and, if so, which therapeutic regimen(s) should be studied.

Conclusions

The authors believe that, until the issues raised above have been further clarified, it seems prudent to strictly limit conclusions from the WHI to the interpretation that initiation of treatment with continuous, combined, oral conjugated estrogen and MPA to HRT-naive women many years into the menopause for prevention of heart disease is inadvisable. Further generalization to conclude that no HRT paradigm will be useful for coronary disease prevention is unjustified and may well be incorrect. The best available clinical evidence on this question remains that from the observational studies, which generally show significant overall benefit in those women who initiate therapy for menopausal symptoms. Mechanistic and animal data provide biological plausibility for a beneficial effect of estrogen given early and further suggest that the randomized controlled trial data from late-start treatment studies (HERS and WHI) may be misleading regarding early-start HRT. The overwhelming evidence favoring use of statins, aspirin, and certain antihypertensives in appropriate secondary and high-risk primary CHD prevention settings is often cited as a reason not to consider HRT for preventive use. This would be reasonable, however, only if the vast majority of coronary events occurred in persons eligible for these treatments, or if HRT could not have benefits additive to conventional atheropreventive measures. Neither has been shown to be the case. Therefore, the existence of good non-hormonal preventive approaches in no way precludes use of HRT, especially in women for whom standard preventive drugs either are not indicated, or will not likely prevent all atherosclerotic events. Given the above, we recommend that the decision to prescribe or not prescribe HRT continue to be individualized in the context of the patient's age, symptoms, BMI, smoking history, lipid profile, bone density, prior history, family history, and other factors. We further recommend that decisions regarding long-term continuation of HRT, previously started at menopause, be individualized in light of the same factors.

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