

Perspectives on the Women's Health Initiative Trial of Hormone Replacement Therapy

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The premature termination of one comparison in the Women's Health Initiative primary prevention trial due to stopping rules being reached necessitates a reconsideration of hormone replacement therapy (HRT). This part of the Women's Health Initiative trial, however, examined only one popular HRT regimen (conjugated equine estrogen [0.625 mg] and medroxyprogesterone acetate [2.5 mg] daily) in asymptomatic postmenopausal women. To help clinicians understand this large, complex trial, we describe several pervasive biases in earlier observational studies, review the principal findings of the trial, summarize recent systematic reviews, and offer clinical suggestions for HRT. Observational studies of HRT have found consistent, powerful protection against heart disease; this now appears due to consistent, powerful selection biases. These biases have the same net effect: Women using HRT in observational studies were healthier than those not using it. The Women's Health Initiative trial found that the overall risk-benefit ratio tipped against using HRT for prevention. Cardiovascular disease and breast cancer were increased among users, whereas colorectal cancer and osteoporotic fractures were reduced. Whether these findings relate to women with menopausal symptoms and to different HRT regimens is unknown. Hormone replacement therapy remains the best treatment for menopausal symptoms. Although estrogen has proven benefit for osteoporosis prevention, alternatives include raloxifene, alendronate, and risedronate. For women needing HRT, use of a low dose, with reassessments at least annually, appears prudent. Heart disease prevention strategies of proven value include exercise, weight control, blood pressure and lipid control, and avoidance of smoking. Hormone replacement therapy

should not be used for this purpose. (Obstet Gynecol 2002;100:1344-53. © 2002 by The American College of Obstetricians and Gynecologists.)

In July 2002, the premature halt of one part of the Women's Health Initiative randomized controlled trial¹ stunned the medical world. The paradoxical finding of increased overall risk associated with conjugated equine estrogen plus medroxyprogesterone acetate in healthy postmenopausal women (Figure 1) led the Data Safety and Monitoring Board to terminate the comparison with a placebo. The aftershocks reflected the scope of this decision: Millions of women have used these hormones,² and the results contradicted an extensive literature from observational studies—as well as experts' opinions.³ Postmenopausal use of estrogen and progestin had consistently been associated with a 35–50% reduction in cardiovascular disease,⁴ leading many to conclude that this therapy could postpone the adverse effects of aging on the heart.

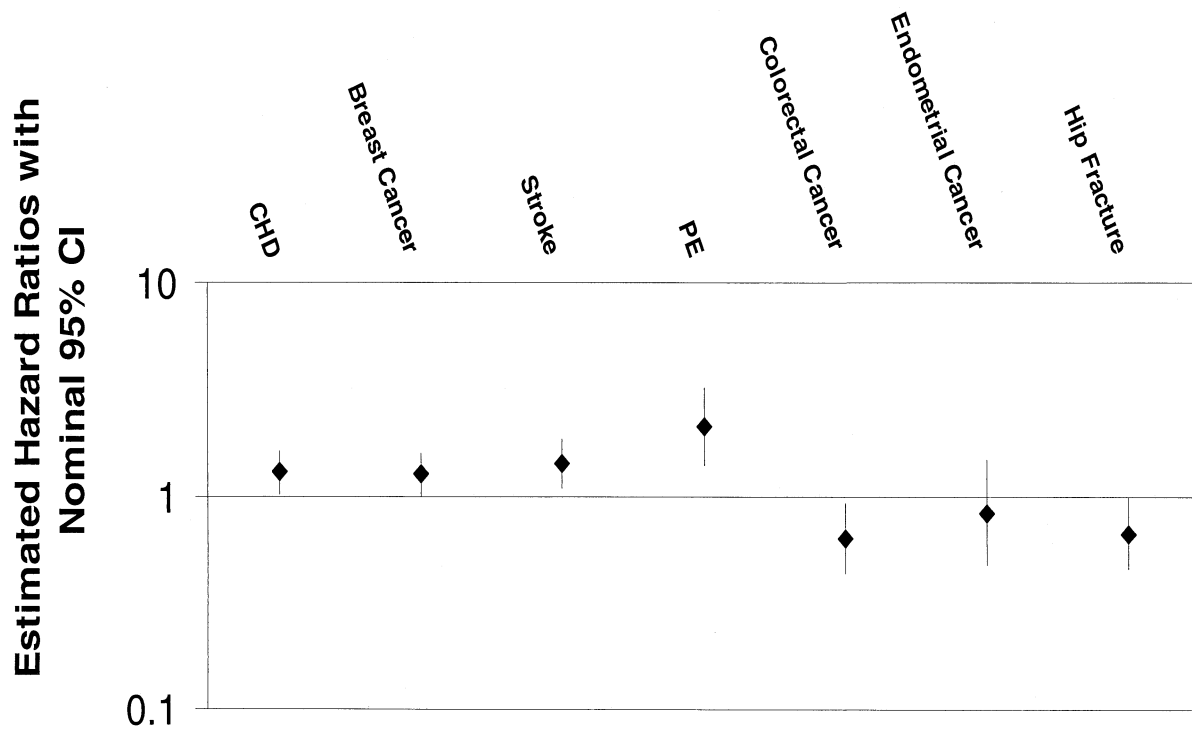
Are the results of the Women's Health Initiative credible? If so, how could prior assessments of the health effects of hormone replacement therapy (HRT) have been so different? To address these concerns, we describe several biases inherent in observational studies, review the methods and results of the Women's Health Initiative trial, summarize recent systematic reviews of HRT, and suggest options for women and clinicians in light of the Women's Health Initiative trial's findings.

PRIOR STUDIES

Both strong basic science and clinical data suggested that estrogen benefits the cardiovascular system in older women. Estrogen receptor (α or β)–mediated mechanisms, both genomic and nongenomic, have been shown to improve lipids, enhance endothelial function, dilate coronary arteries, and inhibit the progression of atherosclerosis.^{5–9} Basic laboratory studies and prospective trials in animals as well as in postmenopausal women have shown this benefit with a variety of surrogate end points. In addition, strong epidemiological evidence exists for a protective effect of estrogen against cardiovascular morbidity and mortality. Several observational studies concluded that the reduction in all-cause mortality in estrogen users (25–50%) was largely attributable to a reduction in cardiovascular deaths.^{10–12}

The population in the Women's Health Initiative trial may have already developed substantial atherosclerosis and thus might not have been able to respond to HRT. In other studies, the putative beneficial effect of estrogen was most evident in younger healthy women who had begun estrogen replacement therapy (ERT) or HRT at

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Major Clinical Outcomes

Figure 1. Estimated hazard ratios for major clinical outcomes in the Women's Health Initiative trial of hormone replacement therapy. CHD = coronary heart disease; PE = pulmonary embolism. Source: Writing Group for the Women's Health Initiative Investigators.¹

Grimes. *WHI Trial Perspectives. Obstet Gynecol* 2002.

the onset of menopause, primarily for the relief of vasomotor symptoms. The highly protective effect seen in the Nurses' Study cohort¹³ occurred predominantly in such women. Trials carried out in monkeys have shown a 50–70% protective effect against coronary atherosclerosis when ERT or HRT is begun at the time of oophorectomy; in contrast, delaying hormone therapy for even 2 years negates this protective effect.¹⁴

However, seeds of scientific skepticism about HRT were planted as randomized controlled trials became the measure, rather than observational studies. In the Heart and Estrogen/Progestin Replacement Study trial¹⁵ (a secondary prevention trial in older women with established cardiovascular disease), HRT was ineffective in preventing the progression of coronary artery disease, particularly if statins and other cardiac medications were already in use. No benefit of ERT or HRT was seen in an angiography end-point trial in the United States¹⁶ and in other secondary prevention trials in the United King-

dom and Germany.¹⁷ The differences in types and regimens of HRT in the above trials suggest that this lack of benefit in secondary prevention is not dependent on the hormonal preparation.

Smaller trials in postmenopausal women, using surrogate end points, have also pointed out that in older women with established coronary heart disease and related medical conditions estrogen is no longer beneficial, in contrast to these effects in younger healthy women.^{18,19} Why aging and progressive atherosclerosis impede the apparent ability of estrogen to protect is unclear but may reflect inability to alter the endothelium, once covered substantially by atherosclerotic plaque; inability to amplify the beneficial effects of powerful cardiac medications; inability for estrogen to work as effectively because of methylation of the promoter region of estrogen receptor α^{20} ; or inability to demonstrate any overall benefit when some women have an early detrimental effect.

SHORTCOMINGS OF SURROGATE MARKERS

For logistical reasons, investigators often study surrogate markers,²¹ such as laboratory tests,²² instead of primary clinical outcomes (eg, illness or death). Unless compelling evidence supports the use of surrogate markers as valid predictors of illness, the primary outcome should always be the focus of clinical research.

Serum lipids are a frequent surrogate marker in cardiovascular research; they can also be misleading. Based on laboratory measurements, clofibrate and similar drugs were recommended for persons with elevated cholesterol. A recent meta-analysis confirmed that this treatment lowered overall cholesterol levels by 10% and, in turn, deaths from coronary artery disease by 9%. However, the unanticipated finding was that these drugs increased the risk of death from other causes by 24%, yielding a net 1% increase in deaths. Adverse effects nullified the benefit of cholesterol lowering.²¹

In the Women's Health Initiative trial, HRT increased high-density lipoprotein cholesterol and decreased low-density lipoprotein cholesterol when compared with a placebo. Paradoxically, even with these beneficial changes, an increased risk of heart disease occurred.¹ Likewise, the Heart and Estrogen/Progestin Replacement Study trial observed similar beneficial changes in serum lipids without a corresponding reduction in illness.¹⁵ The same result held true after additional years of unblinded follow-up.²³ The Postmenopausal Estrogen-Progestin Interventions Trial⁵ found that HRT improved serum lipids, although this trial did not examine clinical outcomes.

Serum lipid changes in younger women taking oral contraceptives present a similar paradox. In the 1980s, oral contraceptives containing norethindrone were touted as having fewer adverse effects on serum lipids than did those containing levonorgestrel, which implied greater safety.²⁴ When investigators addressed the primary outcome of interest, myocardial infarction, they found no significant difference in rates between users of either type of pill.²⁵ Changes in women's serum lipids induced by exogenous steroids simply do not predict clinical illness.

Bone mineral density is a common surrogate marker for fracture. Fluoride, which can increase bone mass, became popular for treating osteoporosis. A randomized controlled trial confirmed that fluoride significantly increased bone mineral density in the lumbar spine (by 35%). Paradoxically, new vertebral fractures were significantly more frequent in the fluoride-treated group. As the vertebrae got denser, they also became more brittle and vulnerable to fracture.²⁶ In contrast, another trial found that slow-release sodium fluoride reduced the risk

of new vertebral fractures.²⁷ These and other examples²¹ point out the need for research that focuses on primary outcomes.

WOMEN WHO TAKE HRT: HEALTHY, WEALTHY, AND WELL EDUCATED

Selection biases probably account for the putative cardiac benefits of HRT seen in most observational studies.²⁸⁻³⁴ Women who choose to take HRT differ from other women; these differences, rather than HRT, likely accounted for the better outcomes. Simply put: Women who choose to use HRT are healthier, more affluent, and better educated than those who do not take these hormones (healthy user bias). These women are younger, leaner, more likely to use alcohol (which in moderation appears protective), more active physically, and less likely to have a worrisome family history, to smoke cigarettes, and to have diabetes. Attempts to control for these potentially confounding effects have apparently been inadequate to date.

Adherence bias²⁸ alone could account for the beneficial effect of HRT seen in observational studies.³⁰ Women who faithfully take their medicines (including those taking placebos) have a lower risk of coronary artery disease than do women who are not adherent to the regimen. Adherence with pill taking is a marker for personal characteristics that confer powerful protective effects, independent of the medication prescribed.

Surveillance bias may play a role as well.²⁹ Women receiving HRT, available by prescription only, are likely to have more frequent contacts with clinicians than women who do not take these hormones. Thus, risk factors for (eg, hypertension) and early indications of coronary disease are more likely to be detected and treated in HRT users.

Survivor bias is yet another explanation for the apparent benefit of HRT in observational studies.³⁵ Women who develop intercurrent illness are likely to stop their HRT, either on their own or at the direction of a clinician. Such women have a markedly increased risk of death.³⁶ Because of this winnowing, women who continue on HRT have a substantially lower risk of disease and death than do women not taking HRT. Each of these biases leads to a spurious benefit of HRT.

Because of inherent biases, observational research often reaches favorable (but incorrect) conclusions. Strong benefits are more common in observational research than in experimental research.³⁷ Systematic reviews that include biased, poor-quality studies often find benefit, whereas reviews that exclude such studies do not.^{2,28} Hence, randomized controlled trials, the only known

way to avoid the selection biases in research, should be done whenever possible.³⁰

TRIAL VALIDITY

Randomized controlled trials have two types of validity: internal and external. Internal validity implies that the trial answered the question it set out to answer. Stated alternatively, is the trial free of bias that might have distorted the results? The gold standard for assessing trial quality is reflected in the CONSORT guidelines.³⁸ Major elements include a sample size large enough to find important differences, truly random assignment to treatments, concealment of the upcoming assignment from those involved with the trial, use of a placebo treatment, minimizing losses to follow-up, and use of an intention-to-treat analysis.

In these important respects, the Women's Health Initiative trial used excellent methods. The sample size was designed to have 88% power to detect an overall 21% lower coronary heart disease incidence in the group receiving HRT over an average of 9 years.³⁹ In the HRT comparison, 16,608 women with a uterus took part. Randomization was done by random permuted blocks, stratified by center and age of participant. Allocation concealment was achieved by dispensing medications in pill bottles labeled only with a number and a bar code. Clinicians and participants were blinded as to treatment assignments. Losses to follow-up were uncommon, only 3.5%. All primary analyses used time-to-event methods and an intention-to-treat analysis.¹

External validity is the ability to extrapolate the trial's findings to other women. Are participants in the trial similar to those in one's practice? Stated alternatively, are participants so different that one could not reasonably generalize the findings? Women enrolled in the Women's Health Initiative trials were 50–79 years old at recruitment and of diverse ethnic backgrounds.

However, participants were not typical users of HRT. Women enrolled were asymptomatic and older (mean 63 years) than many women who take HRT (commonly in their early 50s). The Women's Health Initiative trial was designed to enroll 10% of women aged 50–54 years and 20% aged 55–59 years, so about a third of women studied were in their 50s.³⁹ However, because the trial results were uniform across different age groups, these findings appear capable of extrapolation to asymptomatic women aged 50–79 years. Nevertheless, information is lacking about the age at menopause for these women, which has important implications regarding their inherent cardiovascular status. Whether the findings can be generalized to symptomatic women at the onset of menopause is unknown.

Was the focus on asymptomatic women a mistake? Although HRT is widely used for the established indications of menopausal symptoms and osteoporosis, many physicians have been prescribing HRT for other off-label uses. In one survey, 41% prescribed HRT for high cholesterol levels and 66% for coronary heart disease. Hence, primary prevention of cardiovascular disease was the focus of this component of the Women's Health Initiative trial.⁴⁰

Another concern is whether these HRT results can be extrapolated to other regimens. The only HRT product studied was conjugated equine estrogen (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg), taken on a daily basis. Whether different estrogens and progestins, different routes of administration (such as transdermal or vaginal), or different combinations of steroid and route would have yielded similar results is unknown. However, the product selected for study was carefully considered before the trial began. For statistical considerations, only one estrogen could be studied, and conjugated equine estrogen is the most widely prescribed in the United States.³⁹ The dose of 0.625 mg was chosen as the minimum effective dose for preserving bone density. For reasons of convenience and bleeding patterns, a continuous daily progestin dose was selected over a cyclic regimen.³⁹

Internal and external validity are relevant to earlier observational studies as well. For example, the cardiovascular benefit of HRT seen in observational research may (because of biases) be apparent and not real (poor internal validity). Alternatively, HRT may have real cardiovascular benefit in symptomatic women early in the menopause, yet this finding may not relate to older, asymptomatic women (good internal validity but poor external validity).

CLINICAL OUTCOMES: CARDIOVASCULAR DISEASE

With aging, even in the absence of a documented cardiac event such as a myocardial infarction, women have substantial atherosclerosis. Based on the monkey model,⁴¹ the diminished ability for estrogen to inhibit coronary atherosclerosis can occur as early as 6 years after menopause if no hormones have been administered. This is aggravated if other cardiovascular risk factors exist. In the Women's Health Initiative trial 36% of women assigned to HRT had hypertension, 49% were current or past smokers, and 34% were obese (body mass index > 30 kg/m²). A perspective to be considered, therefore, is that not all women were healthy: For many, the HRT intervention was in the setting of a secondary (not primary) prevention trial.

In the first 2 years of the Women's Health Initiative trial, more cardiac events occurred in the HRT group (Figure 1). This is consistent with the findings of the Heart and Estrogen/Progestin Replacement Study¹⁵ and other secondary prevention trials. Even in the Nurses' Study, when a subgroup analysis was carried out to examine only those women with documented coronary disease, an increase in cardiovascular events occurred in the first 2 years in that group,⁴² followed by a reduction in events as well as mortality. Thus, in the Women's Health Initiative trial and traditional secondary prevention trials an "early harm" effect is evident with standard doses of HRT in the first 2 years. Although the explanation is unclear, some have speculated that because this does not happen in women receiving statins concurrently,⁴³ HRT (in the doses used) may lead to plaque destabilization. Among women who have been receiving estrogen for some time, those who sustain a myocardial infarction are less likely to die as a result.⁴³

The Women's Health Initiative also confirmed a two-fold increase in venous thrombosis and pulmonary embolus (again occurring early) in women receiving HRT. These data are similar to the findings in the Heart and Estrogen/Progestin Replacement Study as well as more recent epidemiological studies.⁴⁴⁻⁴⁶ Pulmonary emboli tend to occur early in women receiving these doses of HRT and, in terms of absolute risk, result in a frequency of 20-30 cases per 100,000 women. By comparison, during pregnancy this risk is 60 per 100,000 women.

In the Women's Health Initiative trial, the risk of stroke was increased to the range reported previously.⁴⁷ Others, however, have reported a protective effect of estrogen.^{48,49} In the Nurses' Study,⁴⁷ although the overall increased risk was of borderline significance, a dose effect was evident, with conjugated equine estrogen (0.3 mg) showing no detrimental effect and conjugated equine estrogen (1.25 mg) showing a statistically significantly increased risk.

BREAST CANCER

The potential association between ERT or HRT and breast cancer has received intensive scrutiny over the years.^{50,51} The findings of the Women's Health Initiative are consistent with a small increase in risk (26%) (Figure 1). No increase in the risk of in situ cancers was evident. In the largest meta-analysis,⁵² the risk of breast cancer was related to duration of use (with standard doses of estrogen) and was compatible with the findings of the Women's Health Initiative trial.

Women who develop breast cancer during or after HRT appear less likely to have metastatic disease. In the largest meta-analysis, the risk of metastases among

breast cancer patients who had used HRT was significantly decreased⁵²; this suggests that these cancers were localized to the breast and potentially had a better prognosis. Corroborating evidence comes from a meta-analysis of HRT and breast cancer deaths.⁵³ Similarly, women who develop breast cancer after use of oral contraceptives are significantly less likely to have metastatic disease. Although this observation could be due to detection bias, a beneficial effect of the steroids themselves on the cancer is another possible explanation.

Addition of progestin to estrogen may increase the risk of breast cancer over that of estrogen alone.⁵⁴⁻⁵⁶ Although the numbers were relatively small, ERT did not show a significant increase in risk, whereas HRT did. Final data on ERT are not yet available from the Women's Health Initiative trial.

FRACTURES

For many years, observational data have linked use of ERT or HRT with a reduction in vertebral and hip fractures.^{57,58} Although a prospective clinical trial showed a reduction in vertebral fractures with transdermal estradiol,⁵⁹ no confirmatory prospective data for hip fractures had been available until the results from the Women's Health Initiative. Because bone mineral density changes do not always correlate with fracture incidence, the results of the Women's Health Initiative are helpful in confirming that HRT reduces hip fractures. Before this, the only agents that reduced hip fracture rates in clinical trials were bisphosphonates—specifically, alendronate.⁶⁰ Raloxifene reduces vertebral fractures, but not hip fractures.⁶¹

In the Women's Health Initiative trial, the nominal statistics showed a significant reduction in vertebral, hip, and total fractures (Figure 1). Of note, women were excluded from participating in the Women's Health Initiative if they had had fractures (severe osteoporosis). Thus, an older population with severe osteoporosis might have enjoyed greater protection from fractures with HRT.

COLORECTAL CANCER

The Women's Health Initiative trial also corroborates epidemiological studies suggesting that estrogen reduces the risk of colorectal cancer.^{62,63} Some studies have found greater protection with increasing duration of use. Although the mechanism(s) are unclear, the confirmation of this protective effect in a randomized controlled trial eliminates the concern of a "healthy user effect," which has been a criticism in assessing the observational

data. Stated alternatively, the effect appears to be real and clinically important.

CONCERNS VOICED BY SOME CLINICIANS

Was the Women's Health Initiative trial stopped prematurely? Some have noted that the adjusted 95% confidence intervals for many outcomes crossed 1.0, indicating a lack of statistical significance at the traditional .05 level. The stopping rules in the Women's Health Initiative trial were not based on the frequency of any single outcome. In an earlier publication,⁶⁴ the investigators pointed out that stopping rules in a prevention trial should be different than those in a treatment trial. The focus of this prevention trial was on a global assessment of health, rather than on any single outcome. This was necessary because an intervention might reduce the risk of one disease while simultaneously increasing the risk of others. Thus, the net health effect should determine the safety of the prevention strategy. Careful planning, conducted in concert with the Data and Safety Monitoring Board of the trial,⁶⁴ led to the global index of health and the modification of the O'Brien-Fleming stopping rules⁶⁵ ultimately used. To have continued the trial to its planned length of follow-up would have been unethical,⁶⁶ given that the specified threshold for stopping had been met.

Because so many participants in both treatment arms quit their treatments early, are the conclusions still valid? The proportions of women who discontinued their treatments were 42% and 38% in the active and placebo arms, respectively.¹ In any randomized controlled trial, all one can evaluate is the policy of giving the intervention. In clinical practice, a large proportion of women will discontinue HRT. In this respect, the Women's Health Initiative trial reflects actual practice. Of importance, participants who quit their medications were not lost to follow-up but were kept in the trial and analyzed in the groups to which they were initially assigned (the proper way of dealing with lack of adherence). Similarly, 6% and 11% of women in these two arms, respectively, initiated hormone treatment from their own clinicians during the trial. Unlike loss to follow-up, lack of adherence to the assigned regimen does not threaten trial validity.⁶⁷

Others have suggested that the large disparity in successful blinding of treatments may have undermined the results. Among those assigned to HRT, 41% learned of their treatment, in contrast to 7% assigned to a placebo (largely due to bleeding differences). Blinding is important when subjective outcomes are the focus of a study (eg, pain, erythema). With objective outcomes, such as myocardial infarction and breast cancer, blinding be-

comes less important.⁶⁸ Indeed, blinding sometimes cannot be used at all when treatments differ greatly (eg, medical versus surgical treatment). In the Women's Health Initiative trial, disclosure of the assigned treatments is unlikely to have led to differential reporting of the outcomes.

UNANSWERED QUESTIONS

Estrogen may have an important effect on the brain.^{2,69-71} Nine randomized controlled trials among symptomatic women, although not entirely consistent, have demonstrated a beneficial effect on verbal memory,⁷² vigilance, motor speed, and reasoning.² Observational data with important methodological weaknesses also show a significant reduction in the risk of developing Alzheimer disease in users of estrogen.⁷³ However, estrogen does not appear to be of benefit once Alzheimer disease has already been diagnosed. Estrogen's interactions with the brain were not examined in the Women's Health Initiative trial; other randomized controlled trials will be needed.

THE WOMEN'S HEALTH INITIATIVE TRIAL IN PERSPECTIVE

The Women's Health Initiative study is the largest trial of HRT ever conducted. The data are valuable and will continue to be analyzed and reanalyzed in the years to come. However, the results of the Women's Health Initiative trial need to be put into perspective. The results pertain only to this particular regimen (conjugated equine estrogen [0.625 mg] with medroxyprogesterone acetate [2.5 mg]) in asymptomatic women with a mean age of 63 years, most of whom had never used hormones. Importantly, the results do not address symptom relief or quality-of-life issues, which were beyond the scope of the Women's Health Initiative trial.

Another large randomized controlled trial (The Women's International Study of Long Duration Oestrogen After Menopause [WISDOM]) is ongoing in the United Kingdom, Australia, and New Zealand. This trial is comparing conjugated equine estrogen (with or without medroxyprogesterone acetate) with a placebo over 10 years. Both the steering committee and an independent safety panel for the WISDOM study reviewed the Women's Health Initiative trial results and unanimously recommended that the WISDOM trial should proceed.⁷⁴ However, on July 26, 2002, the United Kingdom Medical Research Council, the trial's sponsor, ordered a pause in enrollment to allow an international group of experts to consider the prudence of continuation.⁷⁵

RECENT SYSTEMATIC REVIEWS

Two systematic reviews of the literature concerning HRT appeared soon after the Women's Health Initiative trial report.^{2,28} Prepared as background articles for the third United States Preventive Services Task Force report, these syntheses comprehensively and critically summarize existing medical knowledge. A unique contribution of both was exclusion of poor-quality observational studies from the data synthesis.³⁷ Aside from treating menopausal symptoms, benefits of HRT include reduction in the risk of osteoporotic fractures and colorectal cancer. Prevention of dementia is not yet established. Harms of HRT include coronary heart disease, stroke, and thromboembolism (especially during early use). The risk of breast cancer and cholecystitis increases with longer use.

CLINICAL RECOMMENDATIONS

Hormone replacement therapy remains the most effective treatment of menopausal symptoms.⁷⁶ Clearly, other regimens and routes of administration besides that used in the Women's Health Initiative trial should also be considered: All doses and routes of estrogen administration appear equivalent in treating symptoms. Lower dose regimens may be safer for long-term use, although data are lacking.⁷⁷ Indeed, even in young symptomatic women, combinations of conjugated equine estrogen and medroxyprogesterone acetate at half the doses used in the Women's Health Initiative trial have equal efficacy for vasomotor symptoms⁷⁸ and for preventing bone loss. Hormone replacement therapy should not be used for primary or secondary prevention of cardiovascular disease, and its use carries other risks as well (Figure 1).

Because of synergism, the effects of lower estrogen doses may be enhanced by adjunctive medications (eg, bisphosphonates or statins). Thus, lower doses of ERT or HRT (less than 0.625 mg of conjugated equine estrogen or its equivalent) may be advisable, even from the onset of menopause, and especially for women anticipating prolonged therapy (more than 5 years).

Alternative treatments for menopausal symptoms are not as effective as HRT. Treatments for hot flashes include megestrol, venlafaxine or paroxetine, and clonidine.⁷⁹ Selective estrogen receptor modulators, such as raloxifene, can exacerbate hot flashes in some women. Alternative therapies, such as herbal medications and soy protein, appear to be borderline effective at best.⁸⁰

Hormone replacement therapy prevents osteoporosis,⁵⁸ and it reduced fractures in the Women's Health Initiative trial. Raloxifene, a selective estrogen receptor modulator, prevents osteoporosis and in one trial reduced the risk of spinal fracture but not fracture of the

hip or other sites.⁶¹ Of note, raloxifene appears to reduce the risk of estrogen receptor-positive breast cancer as well.⁸¹ Bisphosphonates, including alendronate and risedronate, maintain bone density similar to HRT and lower the risk of fractures in osteoporotic women.

Each patient's risks, benefits, and preferences should be taken into account, and prescriptions should be written to suit the individual. A treatment plan should be made for no more than 1 year. After a year, adjustments may be made, taking into account individual needs, benefits, and risks as more data become available. For women choosing to discontinue HRT, several approaches to tapering off are available.^{79,82}

Because cardiovascular disease is the leading cause of death,³⁵ lifestyle approaches, including maintaining normal weight, exercising regularly, and avoiding smoking, are recommended for all women.^{8,83} Antihypertensive and lipid-lowering therapy are appropriate for women who cannot achieve desirable targets through lifestyle modification. For women with established coronary artery disease, further medical interventions, such as antiplatelet therapy, beta blockers, or angiotensin-converting enzyme inhibitors, are usually indicated. For prevention of fractures, calcium and vitamin D supplementation, weight-bearing exercise, and avoidance of smoking are prudent for women at risk of osteoporosis.^{84,85}

Hormone replacement therapy has enjoyed wide use for prevention of coronary artery disease.⁴⁰ In contrast, the effective prevention strategies described above have been used too little. This paradox both hurts women's health and squanders precious resources. Better scientific standards^{3,30,86} for clinical decision-making and broader application of evidence-based prevention strategies will improve health for women of all ages.⁸⁵

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Received September 18, 2002. Accepted September 19, 2002.