More and more women are entering their postmenopausal years, requiring more training of women’s health care professionals and greater research efforts to further uncover the benefits and risks of hormone replacement therapy (HRT). In the Western world, menopause occurs at about 51.4 years, and currently close to 42 million women in the United States are older than 50 years [1]. With a life expectancy of almost 80 years [1], most women can expect to spend one third to one half of their lives as postmenopausal women.

During the time from the reproductive years to and beyond the last menstrual period, ovarian function is progressively lost; this loss is accompanied by endocrine, somatic, and physiologic changes. The loss of estrogen that characterizes menopause is associated with vasomotor symptoms (hot flashes and night sweats), sleep disturbances, and urogenital problems [2]. In addition, the loss of estrogen has been associated with an increased risk of cardiovascular disease (CVD) and osteoporosis in postmenopausal women.

Currently, approximately 38% of American women between the ages of 50 and 74 years take HRT [3]. Established benefits of HRT include relief of vasomotor symptoms, prevention and treatment of vaginal dryness and urethritis, improvement in serum lipoprotein profiles, and prevention of osteoporosis [4–7]. In addition, it has been proposed that HRT reduces the risk of cognitive decline [8], depression [9], colorectal cancer [10], and Alzheimer’s disease [8,11]. These potential benefits are currently under investigation. Established risks of HRT use include an increased risk of venous thrombosis [12,13], increased levels of triglycerides [14], and an increased risk of developing gallbladder disease [15].

The big questions about HRT are not about short-term use for vasomotor symptoms and long-term use for prevention of osteoporosis, but about long-term systemic use of HRT and its possible adverse effects. Controversy still remains regarding the role of HRT in CVD and breast cancer [16]. Thus, the goal of this review is to provide the latest information from the literature, analyze the issues, offer guidelines for primary care physicians, and provide information about ongoing clinical trials that may clarify the role of HRT in CVD and breast cancer in postmenopausal women.

HRT and Primary Prevention of CVD

Since CVD is the single leading cause of death among postmenopausal women [17], understanding the potential cardioprotective effects of HRT is critically important. Although data from observational studies largely support the use of HRT in postmenopausal women for reducing the risk of CVD, recent randomized controlled clinical trials have raised more questions about the risks and benefits of HRT. For physicians, these new data make counseling postmenopausal women regarding HRT and CVD extremely complex and challenging.

An impressive body of evidence has suggested that estrogen is cardioprotective. Studies indicate that the rate of coronary heart disease (CHD) is higher in men than in premenopausal women but that the risk for women substantially increases after menopause, a time characterized by low estrogen levels [18,19]. Studies also indicate that an increased risk of CHD is associated with bilateral oophorectomy and that this risk may be prevented by HRT [20]. Mendelsohn and Karas recently reviewed the physiologic effects of estrogen on the cardiovascular system [21]. Data presented in their review suggest that estrogen has both rapid and long-term direct effects on the blood vessel wall. The rapid effects of estrogen, such as vasodilatation, occur within few minutes after estrogen exposure and are not dependent on changes in gene expression. Long-term effects of estrogen, such as inhibition of response to vascular injury and prevention of atherosclerosis, occur over hours or days after estrogen exposure and are dependent on changes in gene expression. Long-term effects of estrogen, such as inhibition of response to vascular injury and prevention of atherosclerosis, occur over hours or days after estrogen exposure and are dependent on changes in gene expression. In addition, estrogen has been associated with favorable changes in several factors that are thought to be markers of CVD. Several studies indicate that high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels as well as plasma viscosity, fibrinogen levels, plasminogen activator inhibitor-1 levels [22], and
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Homocysteine levels [23] are favorably affected by estrogen therapy. Estrogen also has been shown to promote insulin sensitivity as well as better body fat distribution [24] and angiogenesis [25].

Nurses’ Health Study
Since the 1970s, more than 30 case-control and prospective studies have suggested that estrogen prevents heart disease in postmenopausal women [19]. In the Nurses’ Health Study, a prospective, observational cohort study, 70,533 postmenopausal women were followed for 20 years [26]. This study suggested that women who used estrogen alone had a decreased risk of major coronary disease compared with women who never used hormones. In addition, a similar reduction of risk was reported among women taking oral conjugated estrogen alone and those taking estrogen plus progesterin [26]. Furthermore, a meta-analysis of the observational studies suggests that HRT reduces the risk of CHD by 35% to 50% [16]. However, it is possible that this reduction in risk may, in part, be related to bias that may be present in observational studies [27]. For example, women who are prescribed HRT are often healthier than nonusers (selection bias) because they have a healthier lifestyle and they are more likely to have preventive evaluations, which may bias the results in favor of HRT.

PEPI Trial
Since randomized clinical trials are designed to overcome many of the biases that occur in observational studies, several clinical trials of HRT have been completed and several more are currently under way. The results of the first large clinical trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, were reported in January 1995 [14]. This was a randomized, double-blind, placebo-controlled trial of 876 healthy postmenopausal women aged 45 to 64 years. The objective of the PEPI trial was to examine the effect of estrogen alone or in combination with progestin on heart disease risk factors in healthy postmenopausal women. Participants were randomly assigned to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/day; (3) CEE, 0.625 mg/day plus consecutive medroxyprogesterone acetate (MPA), 2.5 mg/day; (4) CEE, 0.625 mg/day plus cyclic MPA, 10 mg/day for 12 days/month; or (5) CEE, 0.625 mg/day plus cyclic micronized progesterone, 200 mg/day for 12 days/month. The women were followed for 3 years and 4 main outcomes were evaluated: (1) HDL and LDL levels, (2) systolic blood pressure, (3) serum insulin levels, and (4) fibrinogen levels. The results from this trial indicate that all active treatments improved LDL levels and lowered fibrinogen levels compared with placebo and that no treatment changed blood pressure or insulin levels. The PEPI investigators concluded that CEE is the optimal regimen for elevation of HDL, that the high rate of endometrial hyperplasia with this treatment restricts use to women without a uterus. Thus, they suggested that postmenopausal women with a uterus who choose to take estrogen should also take a progestin.

EPAT and PHOREA Trials
Two additional primary prevention trials, Estrogen Prevention of Atherosclerosis (EPAT) [28] and Postmenopausal Hormone Replacement Against Atherosclerosis (PHOREA) [29], have addressed the question of whether estrogen inhibits atherosclerosis, a major risk factor for heart disease. EPAT was a randomized, double-blind, placebo-controlled trial of 222 healthy postmenopausal women without preexisting CVD [28]. This study was designed to determine the effect of unopposed estrogen on the progression of subclinical atherosclerosis. Postmenopausal women were randomly assigned to placebo or oral 17β estradiol (1 mg/day). In addition, all women with high LDL cholesterol levels received lipid-lowering medications. The rate of change in intima-media thickness (IMT) of the right distal common carotid artery wall was evaluated every 6 months in the participants during 2 years of follow-up. The results indicated that the average rate of progression of subclinical atherosclerosis was slower in healthy women taking estrogen than in women taking placebo. In subgroup analysis, this result was seen only in women not receiving lipid-lowering medications.

The objective of the PHOREA trial was to test the hypothesis that HRT regimens containing estrogen and progestin inhibit the progression of carotid artery IMT in a population of clinically healthy postmenopausal women (n = 321) who were at increased risk for CHD and stroke [29]. Postmenopausal women were randomly assigned to (1) placebo; (2) 17β estradiol, 1 mg/day plus cyclic gestodene, 0.025 mg/day for 12 days every third month; or (3) 17β estradiol, 1 mg/day plus cyclic gestodene, 0.025 mg/day for 12 days every month. IMT was evaluated for a period of 1 year. The data indicated that use of HRT for 1 year was not effective in slowing progression of subclinical atherosclerosis in postmenopausal women at increased risk. However, LDL and fibrinogen levels decreased in both HRT groups compared with the control group. The authors speculated that the protective effects of HRT on CHD may be mediated by mechanisms other than inhibition of atherosclerosis or that the cardioprotective effects of HRT may require more than 1 year to emerge.

Women’s Health Initiative
The Women’s Health Initiative (WHI) is the first randomized primary prevention trial to directly address whether estrogen and/or estrogen plus progestin has favorable or unfavorable...
effects on CHD incidence among healthy postmenopausal women [30]. The estrogen plus progestin component of WHI trial included 16,608 postmenopausal women (50 to 79 years) with an intact uterus at baseline [13]. Participants were randomized to receive CEE (0.625 mg/day) plus MPA (2.5 mg/day) or placebo. The primary outcome was CHD, the secondary outcome was hip fracture, and invasive breast cancer was designated as the primary adverse outcome. In an attempt to summarize the risks and benefits associated with HRT use, a global index was defined as the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes. On 31 May 2002, after a mean follow-up of 5.2 years, the data and safety monitoring board (DSMB) recommended stopping the estrogen plus progestin part of the WHI trial because the data suggested that women receiving this regimen had an increased risk of breast cancer, and the global index suggested that the treatment was causing more harm than good [13].

The increased risk of breast cancer appeared after 4 years of HRT use, whereas the other adverse outcomes (ie, an increased risk of CHD, stroke, and pulmonary embolism) began appearing within 1 to 2 years. Although the relative risk of breast cancer was increased in the study, the authors point out that the absolute risk of harm to individual women may be very small. The data suggest that over 1 year, 10,000 women taking estrogen plus progestin might experience 7 more CHDs, 8 more invasive breast cancers, 8 more strokes, and 18 more thromboembolic events compared with 10,000 women taking placebo. In addition to potential adverse outcomes, it is important to note that the study results suggest that HRT may have some potential benefits. Women taking HRT had a decreased risk of hip fracture that appeared within 1 year and a decreased risk of colorectal cancer that emerged after 3 years of hormone use. The absolute benefits to individual women may be small because the data suggest that over 1 year, 10,000 women taking estrogen plus progestin might have 6 fewer colorectal cancers and 5 fewer hip fractures compared with 10,000 women taking placebo.

Although the DSMB stopped the estrogen plus progestin arm of WHI, it recommended continuing the estrogen replacement therapy (ERT) arm of the trial for hysterectomy-omized women [13] because there was no current evidence of increased risk of breast cancer in women taking estrogen alone in this trial. Thus, we may have to wait until 2005 (when final results are expected) to know whether the estrogen-only regimen has beneficial or adverse effects in women.

The WHI trial results may provide some data on which to base treatment recommendations for healthy postmenopausal women taking CEE plus MPA. As the authors point out, results from WHI indicate that the combined CEE (0.625 mg/day) plus MPA (2.5 mg/day) treatment should not be initiated or continued for the primary prevention of CVD [13]. However, it is important to remember that the results of this trial cannot be extrapolated to all hormone therapies. A major limitation of this trial was that it tested only one HRT regimen. Thus, results from WHI may not apply to different dosages of HRT, other formulations of estrogens and progestins, other routes of administration (orals versus parenteral), and/or different patterns of administration (continuous versus sequential). In addition, the results of this trial do not enable us to distinguish the adverse and beneficial effects of estrogen from those of progestin. Although we may have to wait until the results of WHI estrogen-only arm are released to begin to understand whether the estrogen, the progestin, or the combination of these drugs is associated with the adverse effects in the WHI, it is important to remember that many of the published observational studies may provide insight into the possible benefits and risks of HRT.

It is possible that MPA may not be the best progestin for use in HRT therapies because data from animal studies suggest that MPA may be associated with adverse outcomes. For example, Adams et al demonstrated that while progesterone had no effect on cardioprotective function of estrogen in female cynomolgus monkeys [31], MPA attenuated the atheroprotective effect of CEE in female cynomolgus monkeys [32]. In this study, CEE treatment (human equivalent to 0.625 mg/day) resulted in a 72% reduction in the coronary artery atherosclerosis, while animals that received MPA (human equivalent to 2.5 mg/day) and/or MPA plus CEE did not differ significantly from controls. In addition, Williams et al [33] suggested that not all progestins act similarly on vascular reactivity. Wagner et al suggested 2 mechanisms whereby MPA might accelerate plaque formation and increase the risk for CHD: by increasing insulin resistance and by facilitating LDLs [34,35].

HRT and Secondary Prevention of CVD

Since several observational studies indicated that HRT may be associated with a reduction in the risk of primary cardiovascular disease, several investigators decided to conduct secondary prevention trials to evaluate whether HRT alters the risk of CHD events in postmenopausal women with established coronary disease.

HERS Trial

The first large randomized, placebo-controlled, secondary prevention trial was the Heart and Estrogen/Progestin Replacement Study (HERS) [15]. A total of 2763 postmenopausal women with coronary disease and intact uteri participated in this trial. Participants were between 44 and 79 years old, predominantly white (89%), and predominantly high school graduates (80%). Women were randomized to receive
a daily dose of 0.625 mg CEE plus 2.5 mg MPA (n = 1380) or placebo (n = 1383) and were followed for an average of 4.1 years. The primary outcomes were the occurrence of CHD events, defined as nonfatal myocardial infarction (MI) and/or CHD death. The results of this trial showed no overall benefits with HRT for the secondary prevention of CHD. In the first year of the trial, there was a 50% increase in risk of CHD in women on active treatment compared with placebo. However, fewer events occurred as the study progressed and some benefits of the therapy were seen by year 4. Numerous explanations have been proposed for the overall null effect of the HERS trial [36–38]. These explanations include: a population of women too old to benefit from the therapy, short duration of follow-up, an inadequate HRT regimen, selection bias, and indications that all important risk factors for CHD were not taken into account. Although this trial did not show early benefits of HRT use, some scientists indicate that we cannot ignore the very marked and statistically significant differences in the impact of HRT over time, which suggest that the early adverse effects of HRT may be coupled with later beneficial effects [38]. In addition, this may be related to early thrombosis and preexisting atherosclerosis while long-term atherosclerosis risk may be diminished.

ERA Trial
Several other secondary prevention trials have been conducted to address whether HRT affects the progression of atherosclerosis among women with established cardiovascular disease. In the Estrogen Replacement and Atherosclerosis (ERA) trial [39], 309 women were randomized to receive (1) CEE, 0.625 mg/day; (2) CEE, 0.625 mg/day plus MPA, 2.5 mg/day; or (3) placebo. Unlike HERS, which used clinical outcomes as endpoints, ERA used changes in coronary diameter (documented by follow-up angiography for 3.2 years) as the primary endpoint. The results of this trial showed no difference in progression of coronary atherosclerosis in women randomized to receive HRT or placebo. In addition, similar results were seen in the group receiving CEE and the group receiving CEE plus MPA, suggesting that the null effect in HERS may not be a function of the use of MPA.

PHASE Trial
Lack of benefit of HRT for the secondary prevention of CVD also was reported in the Papworth HRT and Atherosclerosis Survival Enquiry (PHASE) trial of 255 postmenopausal women with established CHD [40]. Unlike ERA and HERS, this trial used a different form of estrogen (17β estradiol at 2 mg/day), a different form of progestin (cyclic norethindrone acetate at 4 mg/day), and a different route of administration (transdermal). The primary endpoint was admission to the hospital with unstable angina, MI, or death. This trial was stopped after 3 years of follow-up because the rates of death, MI, and unstable angina were greater (although not statistically significant) in the HRT group compared with placebo.

WEST Trial
The Women Estrogen for Stroke Trial (WEST) examined the effect of 17β estradiol (1 mg/day) in postmenopausal women (n = 652) who recently had a transient ischemic attack or stroke. After a mean of 2.7 years of follow-up, there was no difference reported between treatment and placebo groups in the incidence of recurrence of stroke or all-cause mortality [41].

Summary
In summary, several recent trials indicate that HRT is not associated with reduced rates of cardiovascular events in women with existing CVD. This has lead to the recommendation by the American Heart Association (AHA) that HRT should not be initiated for the secondary prevention of CVD [42]. However, the results of these trials may not apply to women using all types of HRT. Further studies, including Estrogen in the Prevention of Reinfection Trial (ESPRIT), the Women's Angiographic Vitamin and Estrogen (WAVE) trial, and the Estrogen and Graft Atherosclerosis Research (EAGAR) study, will further address this question [22,40].

HRT and Risk of Breast Cancer
Many postmenopausal women refuse HRT out of fear that it may increase their risk of breast cancer. The risk factors for development of breast cancer are still a bit unclear, but clues are hemmed in both modifiable and nonmodifiable risk factors, including loss of heterozygosity of tumor suppressor genes such as BRCA1, BRCA2, and p53; lifestyle factors; and hormonal status [43–45]. Since the development of human mammary tissue is tightly linked to estrogen and progesterone levels, the role of these hormones in the proliferation and/or transformation of the postmenopausal mammary epithelium has become the object of extensive studies [46–48]. Observational studies on the association between ERT and/or HRT use and breast cancer risk have been inconsistent and often difficult to interpret [49–54]. Part of the problem in interpreting the evidence on ERT/HRT and breast cancer is that the data often come from observational studies, which have some methodological limitations. During the past 25 years, close to 60 observational studies have been published, yet there is a lack of consistency among studies investigating the association between ERT/HRT use and the risk of breast cancer [49]. Data from some observational studies suggest an increased risk of breast cancer among HRT users. For example, data from National Cancer Institute's Breast Cancer Detection Demonstration Project (BCDDP) suggest that estrogen-progestin therapy is associated with an increased breast cancer risk beyond that associated with...
estrogen alone [50]. The latest report from Nurses’ Health Study is in agreement with the finding from the BCDDP [51]. The Collaborative Group of Hormonal Factors in Breast Cancer reanalyzed about 90% of the worldwide epidemiologic evidence on the relationship between risk of breast cancer and use of HRT [52]. In this study, the type of HRT used was predominantly estrogen alone, with only 12% of women having mainly used estrogen and progestin combined. Most of the 51 studies included in this reanalysis were conducted in North America and Europe. This reanalysis also suggested an increase in breast cancer risk in women using HRT that was marked with longer use. This increased risk was reduced after the use of HRT ceased and largely disappeared after about 5 years.

Interestingly, the breast cancer diagnosed in women who ever used HRT has been shown to be less clinically advanced than those diagnosed in never-users of HRT. In June 2000, Li et al published the results from a population-based case-control study in Washington state [53]. The results of this study suggest that estrogen-progestin use is associated with an increased risk of lobular breast cancer that accounts for 5% to 10% of all breast cancers. However, the risk of ductal carcinoma, which is associated with increased incidence and poorer prognosis compared with lobular carcinomas [54], was not elevated among HRT users. Similarly, Sacchini et al [55] reported that while tumors do occur more frequently in HRT users as compared with nonusers, the tumors in HRT users were less aggressive and less prone to develop metastasis than those seen in postmenopausal women that have been left out of HRT. Furthermore, Nanda et al [56] showed a reduced risk of death from breast cancer in HRT users compared with nonusers. These observations suggest that breast cancer associated with HRT use may have a better prognosis than breast cancer associated with nonuse of HRT.

In contrast to the study reports discussed above, some investigators reported no increased risk of breast cancer among HRT users compared with nonusers. The Iowa Women’s Health Study, a prospective cohort study, indicates that there is no statistically significant increase in the risk of breast cancer in ever-users or current users of HRT after 6 years of follow-up [57]. In addition, a report released after 8 years of follow-up suggested that even current users of HRT with a family history of breast cancer had no significant increase in the rate of breast cancer compared with nonusers with the family history of breast cancer [58]. The data from National Health and Nutrition Examination Survey (NHANES), based on a nationally representative cohort followed for up to 22 years, also failed to find that an increased risk of breast cancer is associated with the use of HRT in the postmenopausal women [59].

The WHI clinical trial was the first randomized controlled clinical trial to directly test whether the most commonly used combined hormone preparation in the United States (CEE, 0.625 mg/day plus MPA, 2.5 mg/day) increases the risk of breast cancer [13]. Results from this trial indicate that after a mean follow-up of 5.2 years, the rate of women experiencing invasive breast cancer was increased by 26% (38 versus 30/10,000 persons per year) while no significant difference was observed for in situ breast cancer. The increased risk of invasive breast cancer did not appear during the first 4 years of HRT use. In subgroup analysis, women with reported prior use of postmenopausal hormones had higher risk for invasive breast cancer than those who never used postmenopausal hormones. In addition, the risk for breast cancer among HRT users was not higher in women with the family history or other risk factors for breast cancer [13].

As mentioned earlier in the CVD section, it is important to remember that the WHI trial tested only one drug regimen and could not distinguish the effects of estrogen from those of progestin. The effects of progestin may be important for the increased risk of breast cancer. This hypothesis is supported by a report from Cline et al, which showed that proliferation of mammary gland tissue in surgically postmenopausal cynomolgus monkeys roughly doubled when MPA was added to the estrogen regimen [60].

The WHI study of estrogen-only use in women who had previously undergone hysterectomy is continuing with no reported increased risk of breast cancer. The results from the estrogen-only trial are expected in 2005 and should help determine whether estrogen-only increases the risk of breast cancer or whether it was the estrogen and MPA combination that increased breast cancer risk.

**Are There Better Alternatives to HRT?**

Because of possible side effects associated with long-term use of HRT, a great emphasis has been placed on identifying alternative, estrogen-related regimens that may be used by postmenopausal women. For example, alendronate, a bisphosphate that inhibits bone resorption, prevents bone loss, increases bone mineral density, and reduces the incidence of fractures, may have similar efficacy but fewer negative side effects compared with some estrogen-progestin regimens in preventing bone loss in postmenopausal women [61]. Similarly, simvastatin, a therapy for hypercholesterolemia in postmenopausal women, may be more effective than some estrogen-progestin regimens [62].

Additional proposed alternatives to traditional HRT regimens include soy phytoestrogens [63] and selective estrogen-receptor modulators (SERMs) [64]. Some studies suggest that soy phytoestrogens possess antioxidant properties [65] and that they may enhance endothelium-dependent vasodilatation and reduce the development of atherosclerosis in rhesus monkeys [66]. Thus, it is possible that these products may be cardioprotective in women [67]. However, clinical trials [68] and observational studies need to directly establish the role of
phytoestrogens in the primary or secondary prevention of CVD and breast cancer in the postmenopausal women.

Studies of SERMs, such as raloxifene and tamoxifen, are currently underway to determine whether these agents can modulate risk of CVD and breast cancer in postmenopausal women [64]. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a clinical trial of postmenopausal women with osteoporosis (n = 7705), raloxifene reduced the risk of vertebral fracture by 50%, reduced the risk of invasive breast cancer by nearly 76%, and did not increase the risk of endometrial cancer [64,69,70]. This study suggested that raloxifene continues to reduce the risk of breast cancer in women with osteoporosis after 4 years of treatment [69]. However, an increased incidence of venous thromboembolism, leg cramps, hot flashes, and peripheral edema were reported more frequently in the women receiving raloxifene compared with women receiving placebo [70]. The Raloxifene Use for The Heart (RUTH) Study is currently testing the effect of raloxifene on primary and secondary prevention of CHD in more than 10,000 postmenopausal women [71]. The RUTH trial also will test the hypothesis that raloxifene reduces the risk of invasive breast cancer in women at risk for a major coronary event. In addition, the Continuing Outcomes Relevant to Evista (CORE) trial is a follow-up to the MORE trial in which breast cancer is the primary endpoint [64]. These trials will provide more information about the benefits and risks associated with SERMs and help us understand whether SERMs may be an alternative to HRT use in some women.

Guidelines for Physicians: How Should the Evidence Be Applied?

Studies demonstrate that both education and advice from health care providers play key roles in women’s decisions about HRT [72–75]. It is important that patients understand menopause, the treatment options available for menopause-related conditions, and the investigations involved in optimizing these treatment options prior to entering the menopause. This allows women to be involved in the decision-making process, thereby improving patient compliance. A discussion of how the patient’s own personal and medical history applies to the known benefits and risks of HRT use and an analysis of how the patient’s history relates to any of the conflicting and evolving data is also important. In this way, the patient and her physician can evaluate an overall benefit or risk of HRT. Reassessment with each yearly visit should therefore be a positive experience yielding the most favorable outcome for the patient.

The WHI trial was the first randomized controlled clinical trial to show that one combined hormone preparation in the United States (CEE, 0.625 mg/day plus MPA, 6.25 mg/day) should not be initiated or recommended for the primary prevention of CHD [13]. In response to the data from this trial, the American College of Obstetrician and Gynecologists (ACOG) offered a preliminary statement [76]. In this statement, ACOG said that HRT continues to be an appropriate alternative for the treatment of acute menopausal symptoms, as short-term use of HRT was not associated with increased risk of breast cancer for up to 4 years. ACOG also suggests that women at risk for CVD who choose to discontinue use of HRT (CEE plus MPA) should be informed about alternatives to HRT, including use of statin drugs and lifestyle modifications, and that women at risk for osteoporosis who choose to discontinue HRT should explore alternative therapies such as alendronate.

Patients should be informed that the WHI study of estrogen-only treatment in women without a uterus is continuing. Although data from this trial will not be available until 2005, the National Institutes of Health stated that there was currently no evidence of increased risk of breast cancer in this arm of the trial [13]. However, women who have not undergone hysterectomy and choose to switch from HRT to estrogen alone should be informed that estrogen alone may increase the risk of endometrial cancer. ACOG has formed an expert working group to review and evaluate the WHI study results and to provide recommendations. It also has formed a task force to review in depth the overall risks and benefits of HRT and to provide detailed clinical practice guidance.

The AHA issued guidelines regarding HRT and secondary prevention of CVD in July 2001 [42]. Based on the secondary prevention trials, HRT should not be initiated for secondary prevention of CVD. Postmenopausal women already on HRT for greater than 1 year who have a history of CVD can remain on HRT if the noncoronary benefits are being realized and patient comfort with HRT continues. With the development of an acute CVD event while on HRT, the decision to continue HRT also depends on the balance between the known benefits and risks and patient preference.

Regarding the breast cancer fear with HRT, women need to be informed about results from the WHI trial [13]. Although WHI tested only one drug regimen (CEE, 0.625 mg/day plus MPA, 2.5 mg/day), all patients on HRT should be aware that this trial suggested a small but significant increased risk of invasive breast cancer. The increased risk of breast cancer did not appear during the first 4 years of HRT use. Also, women should be informed that previous studies suggested that postmenopausal women who develop breast cancer while on HRT have less aggressive tumors, more favorable prognosis, and decreased mortality as compared with women not on HRT [56,58,77]. In addition, women should know that the WHI results may not necessarily apply to different formulations of estrogens and progestins, other routes of administration, and/or different patterns of administration. Patients
Future Directions

Results of the WHI study of unopposed estrogen use in women without a uterus and the Women’s International Study of Long-Duration Oestrogen after Menopause (WISDOM) will provide further information regarding HRT use and primary prevention of CVD, along with further clarity on HRT use and breast cancer risk. Studies examining the different estrogen and progesterone formulations in relation to the risks and benefits of HRT will be useful toward counseling postmenopausal patients. An ongoing discussion of other HRT regimens, other medicines, trial outcomes, and the balance of risks and benefits will assist in future decision making.

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