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CONSENSUS OPINION

Effects of Menopause and Estrogen Replacement Therapy or Hormone Replacement Therapy in Women With Diabetes Mellitus: Consensus Opinion of The North American Menopause Society

ABSTRACT

Objective: Given that the prevalence of non–insulin-dependent diabetes mellitus (type 2 DM) is increasing in postmenopausal women and type 2 DM substantially increases the risk for cardiovascular events in postmenopausal women, a population that is at higher risk for coronary heart disease, The North American Menopause Society (NAMS) developed a consensus opinion on appropriate management strategies for postmenopausal women who have or who are at risk for developing type 2 DM.

Design: NAMS held a closed conference of experts in the field to evaluate the published clinical data on the effects of menopause, type 2 DM, and estrogen or hormone replacement therapy (ERT/HRT) in women, especially the effects on cardiovascular risk factors, and to discuss therapeutic options. The proceedings of the conference were used to assist the NAMS Board of Trustees in developing this consensus opinion.

Results: On the basis of the current knowledge, NAMS established consensus on the following issues: (1) Controlling cardiovascular risk factors through pharmacologic and nonpharmacologic means can significantly decrease the risk for developing cardiovascular events. (2) A broad-based recommendation for ERT/HRT cannot be made; rather, the benefits and risks must be weighed in the context of each woman's risk factors. (3) When ERT/HRT is recommended, the greatest benefits may be obtained from the use of transdermal estrogen preparations, low doses of oral estrogens, progesterone instead of progestin, and/or nonandrogen preparations, although more research is needed in this area. (4) Counseling can help maximize the patient's adherence to multiple medication regimens and increase her understanding of the potential benefits and risks of ERT/HRT.

Conclusions: Controlling an individual woman's risk factors for cardiovascular events should be the focus of any management strategy for a postmenopausal woman who has or is at risk for developing type 2 DM. (*Menopause* 2000;7:87–95. © 2000, The North American Menopause Society.)

Key Words: Cardiovascular risk factors – Estrogen replacement therapy – Hormone replacement therapy – Menopause – Type 2 diabetes mellitus.

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The Board of Trustees of The North American Menopause Society (NAMS) developed this consensus opinion with assistance from the following participants in a closed conference held in New York, New York, on October 16, 1998: Andrea Dunaif, MD (Chair); Wulf H. Utian, MD, PhD (Rapporteur); Suzanne L. Brandenburg, MD; Marie Gerhard, MD; Rogerio A. Lobo, MD; Caren G. Solomon, MD; and James R. Sowers, MD. Edited, modified, and subsequently approved by the NAMS Board of Trustees on October 28, 1999.

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The North American Menopause Society (NAMS) held a consensus conference on the topic of menopause, diabetes mellitus (DM), and the use of estrogen replacement therapy (ERT) and hormone (estrogen plus progestogen) replacement therapy (HRT). The consensus conference was convened to discuss the following issues: (1) the increasing prevalence of non–insulin-dependent DM (type 2 DM) in postmenopausal women, (2) the high rate of

cardiovascular events in these women, (3) the influence of comorbid conditions on both DM and menopause, and (4) the lack of a consensus on how best to balance the benefits and risks associated with ERT/HRT in these women. The objective of the conference was to review data that may have an impact on these four issues and to formulate a consensus opinion of appropriate management strategies for a postmenopausal woman who has or is at risk for developing type 2 DM. The NAMS consensus-building process has been described in a previous issue.[1] In this article, the specific type of diabetes noted in a study is indicated, when known; the term *diabetes mellitus* (or DM) is used when the specific type was not indicated or when it included both insulin-dependent (type 1) and non–insulin-dependent (type 2) DM.

BACKGROUND

Therapeutic options for most women who are at menopause and have a uterus include ERT or HRT to decrease the risk of endometrial cancer associated with unopposed estrogen therapy.[2] After surgical menopause, the use of estrogen plus androgen may be appropriate for selected individuals.

Despite the paucity of controlled studies on the use of ERT/HRT in postmenopausal women who have or are at high risk for developing type 2 DM, it is clear that these women have a substantially higher risk for developing cardiovascular disease—a risk that increases after menopause. Because postmenopausal women who have type 2 DM are at high risk for developing coronary heart disease (CHD), the primary focus of therapy in this population should be to reduce this risk. The use of ERT/HRT as an option is based on observational studies suggesting that it decreases the risk for CHD.[3–6] However, results of the Heart and Estrogen/Progestin Replacement Study (HERS)[7] contradict some of the observational data.

In postmenopausal women who have type 2 DM, the underlying changes in glucose metabolism, vascular physiology, body composition, and lipid profile, as well as the increased risk for endometrial cancer, have an impact on the decision to use ERT/HRT. Moreover, these factors influence the selection of the specific estrogen and/or progestogen, the route of administration, and the concomitant use of nonhormonal therapies.

As women age, they are more likely to develop type 2 DM. At 50–59 years of age, approximately 12.5% of women have type 2 DM; at age 60 years and older, the rate increases to 17–18% (a 25–30% increase).[8] Furthermore, type 2 DM remains undiagnosed in more than one third of these women. Also, the disease is more prevalent in women of non-Caucasian background.

The incidence of obesity also increases as the population ages.[8] Body composition changes with age—a significant reduction in lean body tissue occurs relative to a gain in adipose tissue. In women, the composition change typically presents as an increase in abdominal adipose tissue (central obesity). The presence of abdominal adipose tissue itself increases the propensity toward insulin resistance, which is often linked with dyslipidemia and coagulation abnormalities.[9] The sedentary lifestyle that often accompanies aging may also contribute to obesity.

Obesity and the loss of lean muscle have been shown to have an impact on endogenous glucose and insulin metabolism. Skeletal muscle is the primary tissue responsible for insulin-mediated glucose uptake. This reduction in muscle mass can lead to insulin resistance, as observed in women of ideal body weight in early postmenopause.[10] After menopause, pancreatic insulin secretion decreases and insulin resistance increases compared with premenopausal outputs.[11,12] These changes may be due to a combination of aging and estrogen deficiency. Estrogen deficiency also affects blood flow to skeletal muscle, further compromising an already reduced uptake of glucose.[12]

RISK FACTORS FOR TYPE 2 DM

Traditionally, the prevention of end stage renal disease and blindness has been the primary focus in the long-term management of DM. However, more than half of the deaths in patients with DM are caused by heart disease.[13] That risk combined with the increased cardiovascular risks associated with menopause underscore the importance of reducing risk factors in postmenopausal women who have type 2 DM.

CHD risk

A postmenopausal woman who has DM is three times more likely to develop CHD or stroke than a woman who does not have DM.[13–15] Moreover, a woman who has DM is four times more likely to die from a myocardial infarction (MI) than a man who has DM.[16]

The increased rate of CHD for a postmenopausal woman seems to be due, in part, to the loss of the protection offered by endogenous estrogen. This point is supported by the dramatic increase in CHD seen in women who have undergone surgically induced menopause.[17]

Other risk factors for CHD magnify the risk for CHD from DM alone.[18] The increased rate of CHD in patients who have type 2 DM may be due to a combination of

factors, such as a greater incidence of hypertension and hyperlipidemia, as well as an elevated body mass index (BMI).[18–20]

Patients who have DM have twice the rate of hypertension; higher levels of total cholesterol, low-density lipoproteins (LDL), and triglycerides; and lower levels of high-density lipoproteins (HDL) compared with those who do not have DM.[21,22] Menopause increases lipoprotein A concentrations, increases oxidation of LDL, and changes LDL particle size to more of an atherogenic form.[23,24] Although not implicated directly as a cause of type 2 DM, these menopause-related factors contribute to the comorbid conditions associated with the disease, such as CHD.

Other CHD risk factors that are common in patients who have DM include the following:

- Obesity, particularly central obesity and high waist-to-hip circumference ratio (WHR).[25]
- Hyperinsulinemia. This is characteristic of type 2 DM, and it predicts occurrence of CHD in men, although its association with CHD in women remains questionable.[26]
- Increased fibrinogen levels, increased plasminogen activator inhibitor-1 levels, and platelet hyperaggregability. These may predispose the patient to the development of thromboemboli.[27] Although risk for developing venous thromboembolism (deep vein thrombosis or pulmonary embolism) does not seem to be higher in patients who have DM,[28,29] the risk for coronary thrombosis is an important consideration.
- Diminished nitric oxide bioavailability. This promotes atherogenesis through decreased leukocyte adhesion, increased platelet aggregation, and increased vascular smooth muscle growth.[30] Also, diminished nitric oxide bioavailability may cause constriction of coronary arteries during physical or emotional stress, thus contributing to myocardial ischemia.[31]
- Hyperglycemia. This results in decreased endothelium-dependent vasodilation of arteries,[32] which may impair coronary artery autoregulation by interfering with the oxidation of nitrous oxide, thus resulting in vasoconstriction.[33] Glycosylation of tissue proteins in the setting of hyperglycemia may predispose women to accelerated atherosclerosis.[34–36]

Other morbidities associated with DM

Women who have DM are also at higher risk for several other conditions compared with women of similar age who do not have the disease. Their risk for developing endometrial cancer is approximately twice as high, a risk not completely explained by WHR or BMI.[37,38] The risk for gallstones is 1.6 times higher and is independent of BMI and WHR.[39]

The incidence of breast cancer seems to be similar for women with and without DM.[37,40,41] However, the risk for developing postmenopausal osteoporosis may be lower in women who have DM than in those who do not. Research has shown that women who have DM have a substantially higher bone mineral density and a lower rate of fracture.[42] African Americans and Hispanic Americans are at increased risk for developing type 2 DM;[43] however, they do not have an increased risk for developing osteoporosis.[44]

Questions remain regarding the difference between natural and induced menopause and the role that menopause plays in type 2 DM and its complications. Information is lacking regarding a direct effect of type 2 DM on the onset and severity of menopause symptoms, although one study found no difference in the age at menopause between women who have or do not have type 2 DM.[45]

SCREENING AND EVALUATION

Postmenopausal women who present for initial consideration of ERT/HRT should undergo screening for DM, hyperlipidemia, and hypertension.

- *DM.* The goal of glucose screening is to identify women who are at risk for developing type 2 DM. Screening should be considered every 3 years for all women aged 45 years and older and for younger women who have other risk factors. In addition to age, recognized risk factors for type 2 DM include obesity (BMI $\geq$ 27 kg/m^2), certain ethnic groups (African American, Native American, Hispanic American), family history of DM in a first-degree relative, hypertension, low HDL ($\leq$35 mg/dL) or high triglycerides ($\geq$250 mg/dL), history of gestational DM or macrosomia, and previously identified impaired fasting glucose (110–125 mg/dL) or impaired glucose tolerance (2-h postload glucose 140–199 mg/dL). More frequent screening should be considered when risk factors in addition to age are present. DM is diagnosed when on two or more occasions either the fasting plasma glucose is 126 mg/dL or greater or the 2-h postload glucose is 200 mg/dL or greater.[46]
- *Hyperlipidemia.* In women who do not have type 2 DM and known CHD, desirable lipid levels include a total blood cholesterol level below 200 mg/dL, LDL cholesterol below 130 mg/dL, and HDL cholesterol above 35 mg/dL. If the patient has type 2 DM, with or without CHD, the LDL target is at or below 100 mg/dL.[46]

- *Hypertension.* Target blood pressure in hypertensive patients who have DM is below 130/85 mm Hg, based on recent guidelines.[47] Hypertensive patients who do not have DM have a recommended goal of below 140/90 mm Hg.[47] Blood pressure control to below 130/85 mm Hg is especially important in the setting of type 2 DM,[46] as higher blood pressures increase risks for renal dysfunction and cardiovascular disease in this condition. In the United Kingdom Prospective Diabetes Study (UKPDS), which examined intensive blood pressure control in patients who have type 2 DM as one area (UKPDS 38),[48] a diastolic blood pressure close to 80 mm Hg significantly reduced the risk for stroke and mortality related to type 2 DM.

Depending on the results of initial screening tests, further evaluation in these areas and for associated conditions may be necessary before initiating ERT/HRT. Because women who have DM have an increased incidence of endometrial cancer,[38] use of pelvic ultrasound or endometrial biopsy may be indicated in these women before starting therapy. An endometrial thickness of less than 5 mm generally is considered acceptable.[49] Any unscheduled uterine bleeding in a postmenopausal woman who has type 2 DM must be assessed thoroughly because of the increased risk for endometrial cancer. The patient's medical history also should be reviewed for factors that may predispose her to the development of gallbladder disease, which is more prevalent in those who have DM. Because the risk for breast cancer seems to be similar in women with and without type 2 DM, the standard practice for breast self-examination and mammography is believed to be sufficient.

CARDIOVASCULAR RISK REDUCTION IN WOMEN WHO HAVE TYPE 2 DM

Controlling underlying modifiable risk factors in women who have type 2 DM is a key component in minimizing their risk for developing CHD. In addition, secondary prevention of CHD is extremely important in this group of women.

Glycemic control

Optimal glucose control is a prime goal of therapy in postmenopausal women who have type 2 DM. The HbA1c concentration should be less than 7%.[50] The UKPDS group (UKPDS 33 and 34)[51,52] showed that tight glycemic control with certain antidiabetic agents in patients who have type 2 DM significantly reduced the risk for microvascular complications and MI. The UKPDS study also reported a tendency toward a lower rate of MI (although not of stroke) in tightly controlled patients. Poor glycemic control has been shown to increase the risk for developing CHD threefold, even after adjustment for other CHD risk factors.[15,53] Postmenopausal women who have type 2 DM are more likely to require multiple therapies than premenopausal women who have type 2 DM.[13,15,54]

Blood pressure control

Recent studies have shown that the control of blood pressure (irrespective of antihypertensive agent or combination of agents used) reduces the risk for CHD over a 5-year period in patients who have DM.[48,55,56] In the UKPDS Group 39 study,[57] tight control of blood pressure (mean of 144/82 mm Hg) in patients with type 2 DM, using either atenolol or captopril along with diet restrictions, significantly reduced diabetes-related endpoints, diabetes-related mortality, and microvascular disease, as well as stroke, with a trend toward a decrease in MI. The sixth report of The Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure[47] recommended that blood pressure in patients who have DM be maintained at less than 130/85 mm Hg.

Lipid control

Studies have consistently demonstrated that reductions in total cholesterol and LDL levels and increases in HDL levels are associated with cardiovascular risk reduction. The HMG-CoA reductase inhibitor pravastatin was shown to lower the risk for cardiovascular events in patients with established CHD and average cholesterol levels.[58] The cardiovascular benefit of reducing serum triglycerides is less clear but may be more important in patients who have DM. Both pravastatin and simvastatin have been shown to significantly reduce cardiovascular events in a subset of patients who have DM to a greater extent than in patients who do not have DM.[59,60] In a separate pravastatin study, although all treated patients experienced a benefit, women older than 65 years had a greater benefit from pravastatin therapy than did age-matched men.[61] Thus, women who have DM and elevated cholesterol levels should be treated as aggressively as men, because the presence of DM seems to abolish the protective effect of female gender. The target LDL level for a woman older than 55 years and who has DM but no known CHD is 100 mg/dL or lower.[46]

Lifestyle modification

Weight loss improves the lipid profile and glycemic control in overweight patients who have type 2 DM. As a result of this weight change, a lowered risk for CHD

would be expected; however, further study is needed to verify this risk modification. Weight reduction has been shown to decrease insulin resistance.[9,62–64] Because a weight loss program typically limits the intake of fats, it also aids in improving the lipid profile.

It is widely accepted that tobacco smoking is a major risk factor for the development of CHD. Both peri- and postmenopausal women who have DM should be strongly encouraged to stop smoking.

Use of alcohol in moderation has not been shown to increase the risk for CHD and has been associated with reduced risk for CHD in those who do not have DM.[65] However, in addition to other recognized risks, excessive alcohol consumption may cause hyper- or hypoglycemia[66] and should be avoided.

Exercise has been shown to reduce insulin resistance and improve control of both glucose levels and lipids in patients who have type 2 DM.[67–69] Preliminary data suggest that regular exercise is associated with a reduced risk for CHD in this population.[70] Any peri- or postmenopausal woman who has DM should be encouraged to perform some physical activity on a regular basis. Such activity could be as simple as walking for 20 min three or more times a week. The goal of any exercise program should be lifestyle modification for long-term adherence. Any woman who is unaccustomed to regular physical activity should begin slowly and then increase as tolerance permits.

Aspirin

The use of aspirin to prevent recurrence of MI has become common practice. It has also gained favor as a preventive measure for patients who are at risk for CHD events. A meta-analysis of 145 prospective, controlled trials of antiplatelet therapy[71] estimated that 38 vascular events per 1,000 patients who have DM would be prevented if aspirin therapy were used for secondary prevention. This finding was further supported by the Early Treatment Diabetic Retinopathy Study,[72,73] which demonstrated a significant reduction in CHD risk in men and women with DM who were randomized to aspirin. On the basis of individual considerations, postmenopausal women who have type 2 DM may benefit from the administration of 81–325 mg enteric-coated aspirin once daily for secondary prevention. Aspirin is contraindicated for those who are receiving anticoagulant therapy or have aspirin allergy, tendency for bleeding, recent gastrointestinal bleed, or clinically active hepatic disease.[46]

Estrogen replacement therapy/hormone replacement therapy

ERT has been associated with a reduction in CHD risk in observational studies involving postmenopausal women.[2–5] However, findings in the HERS trial[7] challenged some of those data.

The HERS trial[7] is the only randomized controlled trial that has examined the effect of HRT on the prevention of secondary coronary events. In this study, 2,763 postmenopausal women (mean age = 67 years) with established CHD were randomly assigned to receive either continuous daily therapy of combined conjugated equine estrogens (CEE) 0.625 mg plus medroxyprogesterone (MPA) 2.5 mg or placebo. Patients were monitored for more than 4 years.

Results revealed that this combination therapy did not reduce the risk for MI, CHD death, or other cardiovascular outcomes compared with placebo. By the end of the first year, LDL decreased and HDL increased in the active-treatment group. Also, women who were taking this HRT combination had an increased risk for developing venous thromboembolism and gallbladder disease.

This study, however, had the following shortcomings: (1) It was a secondary prevention trial, and ERT/HRT may have a different impact on CHD in a primary prevention setting. (2) It studied only CEE and MPA. (3) It did not include women who were taking estrogen alone, thus compromising extrapolation of these results to women who are taking ERT and in whom there is substantial observational evidence that cardiovascular events are reduced. (4) The average age of the women in this study was greater than that of women who typically start HRT and may have represented a higher risk group. No information is available regarding the study participants with type 2 DM, who represented approximately 20% of the study population.

Possible interpretations of the HERS trial are that the use of a progestogen (or at least MPA, as prescribed) may attenuate the beneficial effects of estrogen and that continuous HRT may not be the most appropriate regimen for women who have established CHD. Postmenopausal women who are already at cardiovascular risk, including those who have type 2 DM and who are just beginning therapy, may be well advised to avoid continuous HRT. However, postmenopausal women who have been taking continuous therapy with CEE and MPA for several years without problems should not discontinue therapy until more definitive data are available.

In other studies, ERT has been observed to improve endothelial function and blood flow in the coronary artery and other vascular arteries.[74–77] There are few data on effects of ERT/HRT on risk for developing DM, but available information suggests no increase in DM risk in HRT users.[78]

THERAPEUTIC STRATEGIES

A number of therapeutic options, both pharmacologic and nonpharmacologic, are available to manage menopause-related conditions of postmenopausal women who have or are at risk for developing type 2 DM.

Estrogen replacement therapy/hormone replacement therapy

Typically, the short-term use of ERT/HRT is focused on the control of vasomotor symptoms and/or urogenital effects. Long-term use generally centers on the reduction of CHD risk, prevention of osteoporosis, and possible cognitive benefits. In women who have type 2 DM, measures to reduce CHD risk are probably of greatest concern.

The specific agent, dose, regimen, and route of administration of estrogen are especially important in women who have type 2 DM. Transdermal ERT administration may offer advantages over the oral route. Serum triglyceride levels, which are often increased in patients who have DM, are not increased further with transdermal ERT.[79] Moreover, alterations in blood pressure in both nonhypertensive and hypertensive women (viewed as being a rare, if not idiosyncratic, reaction) have been reported only with oral therapy. However, transdermal delivery may sacrifice the potential benefits on fibrinolysis and/or vascular reactivity if liver metabolism is a factor, as well as sacrifice the potential benefits on lipid levels provided by oral ERT. The data on insulin sensitivity are interesting but small scale and, given the UKPDS results,[48] may suggest that modification of cardiovascular risk factors is more important than a small sacrifice in insulin sensitivity and, thus, glycemic control. Although transdermal delivery may be the preferred route of estrogen administration in women who have type 2 DM, some women cannot tolerate transdermal delivery because of skin irritation. It also has the disadvantage of being more expensive than oral ERT.

If an oral estrogen is preferred, a threshold daily dose of 1 mg 17β-estradiol or 0.625 mg CEE, or equivalent, should be used, even if vasomotor symptoms are still present at this dose. Higher doses have not been associated with increased benefit on the lipid profile but have been associated with decreased insulin sensitivity in a small study.[80] Oral ERT has been reported to increase the serum triglyceride concentration,[81,82] which may be problematic in women who have hypertriglycemia or gallbladder or coagulation disorders.

Research suggests that when estrogen is combined with a progestogen (HRT), the beneficial effects of estrogen on HDL, insulin sensitivity, and endothelial function are attenuated or abolished.[83–85] If HRT is required, sequential therapy is recommended, rather than continuous therapy, to minimize exposure to progestogen. The use of a low-dose, oral, micronized progesterone is recommended, although nonoral progesterone formulations (intravaginal or intrauterine) may also minimize the potential for negative metabolic effects. The medroxyprogesterone acetate and norethindrone types of synthetic progestogen should be avoided in women who have type 2 DM.

In women who have type 2 DM and preexisting coagulation disorders or in those who smoke, ERT/HRT should be administered only with extreme caution, and patients should be carefully monitored. Also, women who have type 2 DM and underlying gallbladder disease should be closely monitored for the development of gallstones while taking ERT/HRT.

Androgen therapy

Androgens should be used with caution in postmenopausal women who have type 2 DM. If androgen therapy is required in these patients, methyltestosterone should be avoided. This agent has been shown to decrease HDL levels and may also cause glucose intolerance.[86]

Other prescription agents

Few oral hypoglycemic agents seem to interact with ERT or HRT. According to the Rezulin (troglitazone) prescribing information (Parke-Davis, Morris Plains, NJ, USA), oral contraceptives that contain ethinyl estradiol and norethindrone may be less effective because of liver enzyme induction when used concomitantly with the antihyperglycemic agent troglitazone. However, given the lower hormonal doses used in ERT/HRT, this liver enzyme effect is unlikely to be clinically relevant. A transdermal estrogen product would further minimize any potential interaction, as this delivery system avoids first-pass hepatic metabolism.

Nonprescription therapies

At present, recommendations on the use of phytoestrogens, such as those found in soy products, cannot be made for postmenopausal women who have type 2 DM because of the paucity of clinical trial data. Antioxidants may have a role in CHD prevention in this patient population, but data are inconclusive. In an observational study involving more than 34,000 postmenopausal women,[87] vitamin E intake was associated with a reduced risk for death from CHD. There was no relationship observed between either vitamin A or C intake and CHD mortality.

Nonpharmacologic approaches

Lifestyle modifications may reduce the incidence and symptoms of type 2 DM. Risk reduction measures include eliminating tobacco smoking, participating in regular exercise, eating a healthful diet, losing excess weight, and reducing stress.

Counseling issues

Postmenopausal women who have type 2 DM are likely to be taking multiple medications to treat concomitant diseases, thereby increasing the likelihood of poor adherence to medication regimens. Counseling, therefore, is extremely important in this patient population to maximize adherence to therapy. Patients must also be vigilant in reporting to their healthcare professional any altered uterine bleeding episodes. As with most preventive therapies, the benefits of ERT/HRT may take up to 1 year to occur. Patients should be counseled to ensure that their expectations are realistic.

CONCLUSIONS

In postmenopausal women, type 2 DM substantially increases the risk for cardiovascular events, making it an important health concern. Controlling cardiovascular risk factors through nonpharmacologic and pharmacologic means, such as smoking cessation, weight management, exercise, hypertensive control, and lipid profile alteration, can significantly reduce the risk for developing cardiovascular events. A broad-based recommendation for ERT/HRT use cannot be made, as the benefits and risks of ERT/HRT must be weighed in the context of each woman's concurrent risk factors (e.g., obesity, dyslipidemia, hypertension). When ERT/HRT is recommended, the greatest benefits may be obtained from the use of transdermal estrogen formulations, low doses of oral estrogens, progesterone instead of progestin, and/or nonandrogen preparations, although more research is needed in this area. Counseling can help maximize adherence to multiple medication regimens and increase the woman's understanding of the potential benefits and risks of ERT/HRT.

More prospective outcome studies in this patient population are needed to characterize further the complex interplay of menopause, type 2 DM, and ERT/HRT on cardiovascular risk reduction. Such studies should explicitly state which estrogen or progestogen was administered, and they should control treatment groups for weight (BMI or WHR). Studies using daily doses lower than 0.625 mg CEE, or equivalent, are also needed to identify the minimally effective dose that may reduce CHD risk.

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