Cardiovascular risk in menopausal women and prevalent related co-morbid conditions: facing the post-Women’s Health Initiative era

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Objective: To review scientific publications regarding cardiovascular risk during the menopausal years and that related to currently recognized highly prevalent co-morbid factors within this period.

Methods: Citations were selected from a PubMed search and the authors’ files according to their clinical and experimental relevance.

Results and Discussion: Although experimental and some observational data have supported the fact that estrogens are beneficial for the female vascular system, these positive actions have been challenged by the results of the Women’s Health Initiative trial and the Million Women Study, which demonstrated an increase in cardiovascular risk and related adverse events. The role of hormone therapy for the menopause has shifted from a preventive use to a limited role in symptom management, for which it remains the most effective intervention. Baseline evaluation of menopausal women should include individual cardiovascular risk assessment, including hypertension, dyslipidemia, elevated body weight, and the metabolic syndrome. Concomitantly, new factors influencing cardiovascular risk have been delineated among postmenopausal women, namely sleeping disorders, depression, vitamin D insufficiency, rheumatoid arthritis, sexual dysfunction, stress, and psychosocial factors. Therefore, a new landscape may be recognized for menopausal women management. Precise evaluation and treatment of each factor should be separately assessed to improve quality of life and reduce cardiovascular disease prevalence. At present, cardiovascular risk reduction strategies are a requisite (albeit underused) for menopausal women. These include education in terms of health, healthy lifestyle, and pharmacologic preventive interventions to reduce co-morbid conditions. (Fertil Steril® 2009;92:1171–86. ©2009 by American Society for Reproductive Medicine.)

Key Words: Menopause, cardiovascular disease, hormone therapy, depression, sleeping disorders, vitamin D insufficiency, psychosocial factors, obesity

“Estrogen’s role in clinical cardioprotection remains an open question” (1). Although 5 years have passed since Naftolin et al. (1) stated this, very little has changed regarding menopausal hormone therapy (HT), except for the fact that multiple prevalent co-morbid conditions, which worsen cardiovascular risk (CVR), have been identified in perimenopausal and postmenopausal women. Cardiovascular disease (CVD) remains the main cause of death in men and women in both developed and undeveloped countries (2–4).

Across the industrialized world, women live 5–10 years longer than men because they develop CVD about 10 years later, possibly due to the protective effect of estrogens (Es) on the female circulatory system. Androgens induce circulatory and metabolic deleterious changes in men (5, 6). Experimental and observational data have demonstrated that Es have a cardiovascular protective effect. Despite this, prevention with HT is still controversial as the Women’s Health Initiative (WHI) study demonstrated the negative effects of HT (7, 8). This tumbled down the existing high hopes regarding its positive effects and in turn has caused a changing attitude toward its use among physicians and patients. During the menopausal transition there is an emergence of the characteristics of the metabolic syndrome (METS) (9), which increase CVR, possibly but not totally related to estrogenic deficiency (6). During this transition there are also lifestyle factors and other prevalent health conditions or co-morbidities that increase CVR. Therefore, the new clinical paradigm for the post-WHI era should include and evaluate all of these different aspects within the holistic clinical approach of the menopause.
The objective of this document is to place CVR into the current perspective and discuss the role of currently recognized prevalent co-morbid conditions during the menopausal transition. Hence, a literature search was carried out using PubMed and the authors’ files. Preference was given to the most recent publications when multiple of these reported equal data.

ESTROGENIC CARDIOVASCULAR PROTECTION

Estrogens intervene in several steps of the atherosclerosis process: supporting endothelial cell survival, decreasing cellular apoptosis, and controlling injury resistance (10). Estrogenic cardiovascular protection through plasmatic lipid changes explains only 25% of the effect, hence other mechanisms, supported by experimental and clinical data, should be taken into consideration such as those related to the direct effect of E on vascular endothelial cells, including angiogenic stimulation, endothelial nitric oxide production, and cytokine and inflammatory marker regulation.

Estrogenic deficiency increases endothelial dysfunction and free radical production (10, 11). Endothelial progenitor cells are higher in fertile women than in men but do not differ between postmenopausal women and age-matched men. Estradiol (E2) stimulates endothelial progenitor cell proliferation through the estrogen receptor (ER), suggesting that their higher levels in fertile women (compared with men) reflect the cardiovascular protective effect (12). Vascular endothelium response to ovarian hormones is ER mediated, especially with the beta type, although the presence of both estrogen receptor types has been demonstrated in the endothelium and artery smooth muscle (13). Immunohistochemical staining has revealed similar expression of alpha-ER (α-ER) and beta-ER (β-ER)—and the novel membrane ER GPR30—in postmenopausal female artery smooth muscle (14). Endothelial functional and anatomical alterations have been reported in small arteries from postmenopausal women (15). Steroid hormones, including E2, can mediate rapid actions independent of messenger RNA (mRNA) or protein synthesis. These are nongenomic mechanisms that are relevant in nonreproductive tissues. Thus, E2, through nongenomic pathways, may initiate vasodilatation, stimulate endothelial growth, and protect vessels from atherosclerosis.

Estrogens are vasodilators by increasing nitric oxide synthesis, and decreasing endothelin-1 and angiotensin II production, as well as modulating acetylcholine and serotonin-dependent vessel relaxation, producing increased prostacyclin secretion and calcium channel inhibition (15, 16). Estradiol also acutely modulates vascular activity of vasoconstrictors, such as angiotensin or serotonin, regulating venous endothelin receptor expression and stimulating vasoconstrictor prostanoids (17, 18). In nonatherosclerotic human coronary arteries, E2 induces rapid endothelium-independent vasodilation and enhances bradykinin endothelium-dependent relaxation (17). All of these data point out that nongenomic E2 pathways are very relevant in normal vasodilatation.

The participation of inflammation and its mediators in cardiovascular pathophysiology and atherogenesis seems to be relevant. Cytokines and soluble adhesion molecules have been associated with both risk factors and CVD. Estradiol, through ERs, reduces the synthesis of a series of proatherogenic cytokines and monocyte endothelial cell adhesion (19–21). Plasma levels of inflammatory molecules, such as C-reactive protein (CRP), cytokines (tumor necrosis factor alpha [TNF-α] and interleukin-6 [IL-6]), chemokines, and adhesion molecules, are increased in patients with essential hypertension (22). In vitro, E2 reduces TNF-α secretion and induces vascular endothelial cell apoptosis (19). Estradiol also increases prostaglandin I2 production through cyclooxygenase 2 activation, which reduces both oxidative stress and platelet activation, contributors of atherogenesis. Increased CRP levels have also been reported to be a CVD predictor (23). Among non-HT-using postmenopausal women, those with greater CRP concentrations had deterioration of their metabolic profiles, including lower insulin sensitivity, abdominal obesity, and more triglyceride and lower high density lipoprotein (HDL) cholesterol concentrations. Of women with high CRP levels, 59% had the METS (24). Treatment of mild-to-moderate periodontal inflammation in otherwise-healthy subjects improves endothelial dysfunction and significantly reduces carotid intima–media thickness as measured by echo Doppler (25). These results, although in a small number of individuals, fit well with the hypothesis that inflammation contributes to early atherosclerosis. Estradiol’s anti-inflammatory effect has been confirmed in atherosclerotic plaques of women who died from coronary disease. Thus, vulnerable atherosclerotic plaques increased significantly as women had more years into the menopause. Despite this, the role of ERs during atherogenesis is still unclear (26). It seems quite plausible that the immune system, inflammatory states, and central nervous system responses (i.e., hormones and neuropeptide secretion) to stress and environmental stimuli strongly affect vascular response to gonadal steroid hormones.

Castration decreases plasma antioxidant capacity, implicating higher low density lipoprotein (LDL) cholesterol oxidation, thus being atherogenic (27). Estrogens are antioxidants, which reduce endothelial LDL cholesterol incorporation (11, 28), and therefore are able to explain the antiatherogenic effects of Es. However, we must also bear in mind the classic changes caused by ovarian hormones on the lipid serum profile (1, 6). Mitochondrial dysfunction has been considered a major aspect of aging. The ERs are present in the mitochondria and Es promote mitochondrial efficiency, decreasing cerebral vasculature oxidative stress. In addition, E treatment increases mitochondrial oxidative phosphorylation and decreases reactive oxygen species production (28, 29).

Steroid hormones do not act as simple switches for receptor activation as cell functions depend on the simultaneous activity of many hormones and factors that determine cell specificity (10). Thus, some progestins may interfere with the cardiovascular benefits of Es. Progesterone significantly increases nitric oxide synthesis, whereas medroxyprogesterone acetate (MPA) impairs E2 signaling both in vitro in human endothelial cells and in vivo in rats (30). In addition, MPA can inhibit the protective effect of E2 on the rat myocardium after reperfusion injury (31). Drospirenone possesses characteristics closer to natural P than other synthetic progestins, and may provide certain advantages due to its effect on cardiovascular disease risk factors (32).

ANDROGENS AND THE CARDIOVASCULAR SYSTEM

Androgens are E precursors and maintain different relationships with Es during the reproductive and menopausal years, which have not been considered when analyzing menopause and HT data. Observational studies show that blood T levels are lower among men with CVD, suggesting a possible preventive role for T therapy. Human arteries and veins express aromatase and 5α-reductase, allowing T to be locally converted to E2. In men, aromatase deficiency accelerates atherogenesis (33). Among nonhealthcare-seeking women, aged 18–75 years, T (total and free), DHEAS, and androstenedione (A) levels decreases with age, without a corresponding change in sex hormone-binding globulin (SHBG). Each steroid has a wide range of normality, and mean values declined steepest in the early reproductive years, with a flattening out at midlife and a tendency for a small increase in elderly women. There were no significant changes in circulating
androgens around the menopause in this population (34). The T and adrenal pregnenolones are not independent determinants of serum CRP or lipoprotein lipid levels, whereas SHBG levels have an independent CVD risk profile predictive value and an independent contribution for LDL cholesterol and triglycerides levels during the menopausal transition (35). Body mass index (BMI) and waist circumference among young postmenopausal women were significantly higher in those with total T levels ≥0.49 ng/mL. The T levels were also directly related to waist circumference, blood pressure (BP), CRP, and endothelin-1 levels (36). Among healthy postmenopausal women, those in the highest T quartile had significantly higher total cholesterol, LDL cholesterol, and triglycerides plasma levels, with low HDL cholesterol levels compared with those in the lowest T quartile. This is considered a proatherogenic risk profile (37). Despite this, one must bear in mind that normal values may vary widely. Age-adjusted T (total and free) and A endogenous levels did not change in 651 postmenopausal women from the Rancho Bernardo cohort, with and without previous heart disease at baseline and did not predict cardiovascular death or death from ischemic heart disease during a 19-year follow-up (38). In the same cohort, SHBG levels correlated negatively with fasting plasma glucose, whereas the baseline SHBG quintile was not associated to CVD or ischemic heart disease for the same follow-up (39). However, higher free T and A within the physiological range had been associated with less carotid artery atherosclerosis in both premenopausal and postmenopausal women (40). In a case-control study, higher total T and SHBG levels were inversely related to carotid atherosclerosis in postmenopausal women (41). Endogenous sex hormone levels have also been studied in postmenopausal women undergoing carotid artery endarterectomy. There is an association between low serum androgen levels and severe internal carotid artery atherosclerosis, suggesting that higher physiological levels have a protective role in the atherogenesis process (42). It seems plausible that after the menopause the effect of Es on the cardiovascular system declines, whereas that of androgens increases, and T exerts a protective effect. However, links between androgens in both men and women remain a controversial issue in the cardiovascular system.

**EFFECTS OF HORMONE THERAPY ON CARDIOVASCULAR RISK**

The WHI study was designed to evaluate the efficacy and safety of a low fat diet, two parallel HT studies: conjugated equine estrogens (CEE) (0.625 mg) plus MPA (2.5 mg) for women with an intact uterus and SHBG levels did not change in 651 postmenopausal women from the Rancho Bernardo cohort, with and without previous heart disease at baseline and did not predict cardiovascular death or death from ischemic heart disease during a 19-year follow-up (38). In the same cohort, SHBG levels correlated negatively with fasting plasma glucose, whereas the baseline SHBG quintile was not associated to CVD or ischemic heart disease for the same follow-up (39). However, higher free T and A within the physiological range had been associated with less carotid artery atherosclerosis in both premenopausal and postmenopausal women (40). In a case-control study, higher total T and SHBG levels were inversely related to carotid atherosclerosis in postmenopausal women (41). Endogenous sex hormone levels have also been studied in postmenopausal women undergoing carotid artery endarterectomy. There is an association between low serum androgen levels and severe internal carotid artery atherosclerosis, suggesting that higher physiological levels have a protective role in the atherogenesis process (42). It seems plausible that after the menopause the effect of Es on the cardiovascular system declines, whereas that of androgens increases, and T exerts a protective effect. However, links between androgens in both men and women remain a controversial issue in the cardiovascular system.

Changes that favor procoagulation and anticoagulation deterioration. Although CEE use for 7 years did not protect against myocardial infarctions or coronary death, there seems to be a lower coronary disease risk at treatment initiation among women aged 50–59 years (44). This benefit among young postmenopausal woman fit well in the so-called critical window hypothesis indicating that Es begun later in menopause do not confer benefits to any outcome. In the WHI population CVD were less frequent among women within 10 years compared with those with more than 10 years since the menopause onset. The HT increased the risk of stroke and did not vary significantly by age or time since menopause (45). However, in a subanalysis of the WHI (only Es–placebo), women with bilateral oophorectomy had a significant increase in coronary artery calcium measured by computed tomography (CT) compared with those receiving HT within 5 years of oophorectomy, suggesting that HT may protect against negative cardiovascular changes that increase CVD and future cardiovascular events (46).

Comparing other studies concerning HT and CVR presents difficulties and is possibly due to the hormones administered, age, inclusion criteria, outcomes—among other factors—therefore inclusion of any study into the puzzle becomes difficult. The Women’s International Study of Long Duration Oestrogen after Menopause (WISDOM) was designed to investigate the effect of HT in young menopausal women (aged 45–60 years) and assure results that were relevant to normal HT use. The targeted age group was later modified to 50–64 years and then extended to 69 years. Therefore, population age became similar to that of the WHI. The trial was prematurely stopped at a median 11.9-month follow-up after publication of the WHI study results, and because there was a significant increase in the number of cardiovascular events and venous thromboembolisms (VTE) (47). Results showed that there was no disease prevention benefit, and there are some adverse effects, confirming those reported in the WHI population. Using a similar methodology as in the WHI trial, E-only treatment was investigated among women who had undergone a hysterectomy and compared with the combined estrogen–progestin United Kingdom General Practice Research Database (GPRD) study (48). The GPRD group with uterus used norgestrel instead of MPA as the progestin for combined therapy (last 12 days of the cycle). The results of the E-alone arm were significantly lower for myocardial infarction and breast cancer and higher for colon cancer, a pattern similar to that found for the combined versus the E-alone arm treatment of the WHI study. The increased likelihood for CVD in hysterectomized women was accompanied by higher rates of myocardial infarction, stroke, and VTE compared with the placebo arm of the GPRD study with intact uterus. It seems that the negative effect of HT on CVR seen among those women with hysterectomy may be due to the more adverse initial conditions found among them (49).

Diabetes mellitus shares an important place as a risk factor for CVD; some studies suggest a beneficial effect of Es on diabetes risk. In women with coronary heart disease, fasting glycaemia increased significantly among those assigned to placebo but did not change for HT users (50). Diabetes incidence decreased 35% in the HT group (Table 1). Among HT users, the diminished risk was not influenced by decreased weight change or abdominal perimeter decrease. Furthermore, among women with type 2 diabetes, low-dose oral HT decreases fasting glucose and total cholesterol without adverse effects on glucose clearance, triglycerides, and CRP levels compared with conventional HT (51).

It is known that HT increases VTE risk two- to fivefold. Absolute risk for women in the CEE/MPA arm of the WHI was 3.5/1,000 person-year compared with 1.7/1,000 person-year in the control group.
### Effects of hormone therapy on cardiovascular risk and adverse outcomes.

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<tr>
<th>Authors or Study Acronyms</th>
<th>HT</th>
<th>Population</th>
<th>Results</th>
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<tr>
<td>WHI investigators (7)</td>
<td>CEE + MPA vs. placebo</td>
<td>Women aged 50–79 years without hysterectomy were randomized to the study diet or HT arm. After 1 year of participation subjects were eligible for inclusion in the calcium plus vitamin D arm.</td>
<td>The study (CEE/MPA arm) was stopped earlier because of risks: 26% increase in invasive breast cancer, 29% for coronary events, 41% for stroke, and a twofold risk increase for VTE. Benefits included decreased risk for colorectal cancer 37%, hip fracture 33%, and total fractures 24%. CEE use for 7 years did not protect against MI or coronary death, although there seems to be a lower coronary disease risk among women aged 50–59 years at treatment initiation. In addition a decrease in hip fracture risk and no decrease in colon cancer risk were observed in the CEE-alone group.</td>
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<td>WHI investigators (43, 44, 45)</td>
<td>CEE vs. placebo</td>
<td>Only estrogen treatment in women with hysterectomy.</td>
<td>The estimated absolute excess risk for CHD according to years since menopause was: 6 per 10,000 person-years (≤ 10 years); 4 per 10,000 person-years (10–19 years), and 17 per 10,000 person-years (≥ 20 years). HT increased the risk of stroke (HR 1.32) without significant differences with regard to age or time since menopause. There was a nonsignificant tendency of HT to have a more favorable effect on total mortality in younger than older women. OR with at least 80% adherence to the study (CEE or placebo) was significantly favorable for HT users. Mean coronary artery calcium score after trial completion was lower among women receiving CEE (83.1) compared with those receiving placebo (123.1). OR among women with at least 80% adherence to the study CEE or placebo was lower in women assigned to estrogen than those on placebo.</td>
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<td>Rossouw et al. (45)</td>
<td>CEE vs. placebo; CEE + MPA vs. placebo</td>
<td>Secondary analysis of the WHI trial (both CCE vs. placebo and CEE + MPA vs. placebo arms) aimed to determine whether time of HT initiation may influence its effect on CVD.</td>
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<td>Allison et al. (46)</td>
<td>CCE vs. placebo</td>
<td>Computed heart tomography in 1,064 young postmenopausal women (50–59 years at randomization) after a mean of 7.4 years of treatment (8.7 years after randomization).</td>
<td>The trial was prematurely closed after a median follow-up of 11.9 months due to the publication of early results of the WHI study. The number of VTEs and cardiovascular events increased. There were no statistically significant differences in number of breast or other cancers, cerebrovascular events, fractures, and overall deaths. The results are consistent with the findings of the WHI.</td>
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<td>WISDOM (47)</td>
<td>CEE vs. placebo</td>
<td>Women aged 45–69 years (mean age 62.8 years) were randomized to receive HT or placebo.</td>
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<td>Tannen et al. (48)</td>
<td>CEE</td>
<td>Hysterectomized United Kingdom women were treated with CEE and compared with a combined estrogen-progestin group from the United Kingdom GPRD.</td>
<td>Higher rates of MI, stroke, and VTE in hysterectomized women than in those of the placebo arm of the GPRD study with an intact uterus.</td>
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<td>Kanaya et al. (50)</td>
<td>CEE + MPA</td>
<td>Women with coronary heart disease were randomized to receive daily CEE plus MPA, or placebo to establish the effects on fasting glucose levels.</td>
<td>Fasting glucose levels increased significantly among women treated with placebo but did not change among women receiving HT. Diabetes incidence decreased 35% with HT in women with coronary heart disease (9.5% controls vs. 6.2% HT users).</td>
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<td>Kernohan et al. (51)</td>
<td>$E_2$+norethisterone vs. placebo</td>
<td>Postmenopausal women with type 2 diabetes were randomized to receive HT daily or placebo for 3 months.</td>
<td>HT decreased fasting glucose compared with placebo (-9.4% vs. +2.3%) and total cholesterol (-13.7 vs. +1.0%) without detectable adverse effects on glucose clearance, triglycerides, and CRP.</td>
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<td>Wu (52)</td>
<td>Meta-analysis of potentially relevant studies: risk of venous thrombosis among women using HT (articles published from 1995 to October 2005).</td>
<td>The increased risk of a first episode of venous thrombosis in women currently taking HT compared with nonusers ranged from OR 1.22–4.50. Similar increases for deep vein thrombosis and pulmonary embolism risks were found. The risk of venous thrombosis is highest in the first year of therapy, reaching more than sixfold increase. Women taking estrogen–progestin HT had a significantly greater risk of venous thrombosis than those using only estrogen HT (OR 1.60). Oral and transdermal HT have also significant differences (OR 4.0) for venous thrombosis relative risk. Thrombophilia and overweight were associated with a further increase in venous thrombosis risk.</td>
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<td>ESTHER (53)</td>
<td>Multicentric French study including women with idiopathic VTE (40–70 years) and matched controls taking HT.</td>
<td>Current oral estrogen users compared with nonusers had a significant increase for VTE risk whereas transdermal $E_2$ did not increase this risk. There was no significant association between VTE and micronized P and pregnane derivatives. Norpregnane derivatives were associated with a fourfold increased VTE risk.</td>
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<td>Canonico et al. (54)</td>
<td>Meta-analysis: VTE risk among women using oral and transdermal HT.</td>
<td>Oral estrogen, but not transdermal estrogen, increased VTE risk, especially during the first year of treatment. First time VTE in current oral estrogen users increased (OR 2.5) as compared to nonestrogen users and current transdermal estrogen users (OR 1.2). Past oral estrogen users had a similar VTE risk compared with never users. VTE risk in oral estrogen users was higher in the first year of treatment (OR 4.0) compared with treatment after the year. Transdermal estrogen may be safer in relation to thrombotic risk.</td>
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<td>Hemelaar et al. (55)</td>
<td>Systematic review from 1980 until and including April 2006.</td>
<td>Nonoral (transdermal or intranasal) postmenopausal HT administration appears to decrease lipoprotein(a), cell adhesion molecules, and factor VII levels, whereas other markers including CRP and homocysteine did not change. Potentially unfavorable changes seen after oral HT are substantially smaller with nonoral HT.</td>
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(43). A meta-analysis assessing venous thrombosis risk among HT users showed that the risk for a first time thrombotic episode was increased (Table 1), being similar for venous thrombosis or pulmonary embolism (52). This risk is greater after the first year of therapy, increasing furthermore among E–progestin users, using larger estrogenic doses and the oral route. Age, overweight, and thrombophilias are cofactors that impose an increased risk. The VTE risk would be lower using transdermal Es compared with the oral route according to the case-control French multicenter Estrogen and Thromboembolism Risk (ESTHER) study (53). Compared with non-HT users, oral HT users presented an increased risk, whereas the transdermal route showed a decreased risk. Concerning progestin type, norpregnane derivatives were associated with a fourfold increased VTE risk. Neither micronized P nor pregnane derivatives (including MPA) were associated with this entity (Table 1). A recent meta-analysis on the same matter emphasized that current oral but not current transdermal Es increased VTE risk (54). Current transdermal E users versus nonusers had similar VTE risk. Risk for women taking oral Es was higher during the first year of treatment compared with treatment beyond the first year. The increased risk was similar for E-alone users compared with combined treatment (E plus progestin). In the same meta-analysis, the results from nine randomized controlled trials confirmed the increased VTE risk in women treated with oral E (Table 1). Another recent meta-analytic review also found that nonoral routes related to less CVR as it induces less changes in CRP and potential CVR endothelial marker levels (55).

The effect of HT on the METS, inflammatory or thrombotic variables in postmenopausal women has also been reported in a meta-analysis. The results from 107 trials showed that HT reduced abdominal fat, insulin resistance, new-onset diabetes, LDL-to-HDL cholesterol ratio, lipoprotein(a), mean BP, fibrinogen and plasminogen activator inhibitor-1 levels. Oral HT increased CRP and decreased protein S levels, whereas transdermal HT had no effect (56). A systematic review including 31 clinical trial (11 were conducted to study outcomes such as bone density, fractures, or surrogate end points for CVD) demonstrated that HT was associated with increases in stroke and VTE, whereas other cardiovascular events were not increased. Although most trials studied older patients, increased risk was not related to age. Combined HT increases the risk of VTE compared with E monotherapy (57). More than 121,000 postmenopausal women who participated in the Nurses' Health Study from 1976–2004 were studied to determine stroke risk in young women (58). Compared with women who had never used hormones, stroke risk increased among both E-alone and E–progestin users. Increased risk was present among women initiating HT at younger ages or near the menopause onset, as well as at older ages or more than 10 years after the menopause. There was also a strong relationship between stroke and E dosage, with higher dosages increasing the risk.

**TABLE 1**

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<td>Salpeter et al. (56)</td>
<td>Meta-analysis of studies related to the effects of HT on components of the metabolic syndrome in postmenopausal women published from April 1966 to October 2004.</td>
<td>HT was associated with significant increases in total stroke (OR 1.29), nonfatal stroke (1.23), stroke leading to death or disability (1.56), ischemic stroke (1.29), and a trend to more fatal stroke (1.28). It was not associated with hemorrhagic stroke (1.07) or transient ischemic attack (1.02).</td>
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<td>Sare et al. (57)</td>
<td>Meta-analysis of trials addressing stroke risk among women using HT.</td>
<td>HT was associated with significant increases in total stroke (OR 1.32) and VTE (2.05). Stroke severity was increased with HT (OR 1.31). The addition of P to estrogen doubled the risk of VTE. HT cannot be recommended for primary or secondary stroke prevention.</td>
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<td>Grodstein et al. (58)</td>
<td>Stroke risk among young women using HT: Nurses’ Health Study.</td>
<td>Stroke relative risk for women currently taking estrogen alone was 1.39 whereas for estrogen with progestin it was 1.27. These results are nearly identical to those of the WHI. However, initiating HT &lt;5 years at younger ages was not associated with a clear stroke increase, although this result was based on a small number of cases.</td>
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*Note: Selection of papers from the WHI trials and other studies relevant to the effects of HT on the cardiovascular system.*

CEE = conjugated equine estrogens; OR = odds ratio; HT = hormone treatment; CVD = cardiovascular disease; VTE = venous thromboembolism; MI = myocardial infarction; CHD = coronary heart disease; GPRD = General Practice Research Database; CRP = C-reactive protein; ESTHER = Estrogen and Thromboembolism Risk; HR = hazard risk; MPA = medroxyprogesterone acetate; WISDOM = Women’s International Study of Long Duration Oestrogen after Menopause.

For clinical and practical purposes, these results allow us to recommend the short-term minimal dose nonoral estrogenic route, mainly for the treatment of menopausal symptoms.

**CARDIOVASCULAR RISK ASSESSMENT DURING THE CLINICAL MANAGEMENT OF THE MENOPAUSE**

The CVR assessment among climacteric woman should be individualized. There have been numerous proposed methods of calculating coronary heart disease and stroke risk. The Framingham scale or scoring ischemic events of any type is among these methods. It can give a 10-year coronary risk estimate, considering sex, age, total cholesterol, HDL cholesterol levels, BP, diabetes mellitus, and smoking status (59). The index has some limitations, which will be discussed later. Co-morbidities should also be evaluated to achieve a successful management of the menopause at both short-term and long-term follow-up.

**Hypertension**

Systolic and diastolic BP correlates inversely to age at menopause and positively to the length of the postmenopausal period, suggesting that low levels of female steroids are a major factor for BP elevation (60). There is a direct relation between hypertension and CVR. In subjects aged 40–70 years risk starts at 115/75 mm Hg, doubling with each 20 mm Hg increase for systolic BP and with each 10 mm Hg in diastolic BP (61). Conventional HT does not significantly affect BP values in postmenopausal women. However, hypertension possibly relates to E and androgen balance. For example, there are associations between serum T and systolic BP in perimenopausal and postmenopausal women aged 50–59 years who have a normal BP (62). Another element involved in BP regulation is the renin-angiotensin system and angiotensin II receptors that may influence gender differences. These receptors are protective, especially in women, and may contribute to the beneficial effects on hypertension and CVR, suggesting interactions between gonadal steroids and the renin-angiotensin system. Thus, angiotensin receptor blockers have prominent effects on the renin-angiotensin-aldosterone system and E2 potentiates their effects on BP (63).

Prehypertensive individuals are those with a systolic and diastolic BP between 120 and 139 and 80 and 90 mm Hg, respectively, whereas hypertensives are those with BP equal or higher than 140/90 mm Hg (64). Prehypertension existed in about 40% of postmenopausal women participating in the WHI study (follow-up 7.7 years) and was associated to a 58% higher risk of cardiovascular death, regardless of ethnicity, compared with women with normal BP. The calculated 10-year incidence of cardiovascular events was 3.63% for women with normal BP, 7.11% for those with prehypertension, and 14.16% for those with hypertension. However, increased CVR with prehypertension is smaller than that associated with diabetes (158%) and higher than that related to smoking (34%) (65). The BP (awake and at sleep) was significantly higher among women reporting hot flashes compared with those not (66). Women with vaso-motor symptoms seem to differ from those without symptoms in terms of CVR and response to HT. Thus, flushing was associated to higher cholesterol levels, BMI, and systolic and diastolic BP compared with those without symptoms, suggesting that the presence of menopausal symptoms is associated with a less favorable CVR (67).

Once hypertension is diagnosed, a short-term therapeutic objective is to maintain BP levels below 140/90 mm Hg, which will significantly decrease cardiovascular and renal morbidity–mortality. Prehypertensive management consists in achieving lifestyle changes: decrease in body weight, increase in physical exercise, low salt diet, and low alcohol consumption. The HT containing E2 and drospirenone may control vasomotor symptoms and BP in prehypertensive symptomatic women (31). These effects are obtained very soon after treatment initiation. Unfortunately there are no long-term studies. Hypertension cases must also be managed with a specific pharmacologic treatment. The combination of drospirenone and E2 associated with hydrochlorothiazide is safe and well tolerated in hypertensive postmenopausal women, producing decreased aldosterone and plasma renin activity consistent with a beneficial antialdosterone effect (68).

**Dyslipidemia**

The menopausal transition may be associated with an accelerated increase of total cholesterol and triglyceride concentrations. Premature ovarian failure (POF) is a special situation that determines a shift in lipid profile. Women with POF had significantly higher triglyceride levels, whereas HDL cholesterol levels were borderline or lower. In addition, free androgen index, SHBG, and T concentrations showed significant correlations with triglycerides or HDL cholesterol concentrations (69). A 10-year follow-up of a Norwegian female cohort aged 40–54 years showed that total cholesterol, triglycerides, and the total cholesterol-to-HDL cholesterol ratio increased from premenopausal to postmenopausal status, which was not associated with increased BP or body weight (70). Age-dependent lipid metabolism changes may arise both as a result of biological aging mechanisms and lifestyle factors. Mean total cholesterol, non-HDL cholesterol levels, and the total-to-HDL cholesterol ratio may show age dependency, with maximum values within 60–70 years. Vegetarians showed lower total and non-HDL cholesterol levels compared with the general population. The age-dependent increase of these parameters is less pronounced with vegetarian nutrition and lifestyle (71). Therefore, lipid age-related changes are preventable by nutrition and lifestyle factors.

Physical activity also influences lifetime female metabolic status. Significant inverse correlations exist between physical activity and waist circumference, body fat, BMI, and insulin, CRP and leptin levels. Age positively correlates to BMI, waist circumference, body fat, total cholesterol, LDL cholesterol, triglyceride, leptin, CRP, and glucose levels. Physical activity, despite age, is associated with fewer risk factors for chronic diseases like CVD, type 2 diabetes, and obesity (72). Therefore, regular physical activity may be considered an antidote to these risk factors. In overweight/obese sedentary nondiabetic postmenopausal women, significant correlations were observed between the triglyceride/HDL cholesterol and the hyperinsulinemic-euglycemic clamp, as well as with the homestasis model assessment. In addition, the triglyceride-to-HDL cholesterol ratio significantly correlated with lean body mass, visceral fat, 2-hour glucose test, CRP, and muscle strength. Contrarily, high insulin sensitivity levels were associated with low triglyceride-to-HDL cholesterol ratios (73).

Diabetes mellitus and hypothyroidism must be ruled out among patients with dyslipidemia and treatment aimed to decrease LDL cholesterol levels. Changes in lifestyle are primarily recommended, including a hypocaloric and low in saturated fat and cholesterol diet to achieve total body weight and cholesterol reduction. Increasing physical activity is also suggested, as 30 minutes a day of exercise reduces LDL cholesterol levels 9.3% after 6 months (74, 75). Exercise intensity and baseline triglycerides established the level of LDL cholesterol reduction. Regarding pharmacologic treatments, statins are the first line drug. Other treatment options include fibrates (for hypertriglyceridemia) and nicotinic acid (for hypertriglyceridemia and low HDL cholesterol) (76).
**Overweight and Obesity**

Increased BMI reduces insulin sensitivity and increases systolic BP, especially in women, and is associated with hyperlipidemia and type 2 diabetes (73, 76). Obesity may also contribute to CVR in relation to coagulation and fibrinolysis alterations, arterial circulation thrombosis potentiation, and by increasing VTE (77, 78). Lean and obese women differ in hormonal and biochemical characteristics. Postmenopausal obese women have higher waist circumferences than premenopausal obese women. Total cholesterol and LDL cholesterol levels are high in postmenopausal women; obese women already display elevated levels in the premenopausal period. The SHBG levels declined and free androgen index increased in postmenopausal obese women in comparison with premenopausal obese women.

A meta-analysis including data from 21 studies regarding overweight and heart disease has shown that being moderately overweight or obese increases the risk of developing coronary heart disease events, which are independent of traditional CVR factors. Moderately overweight individuals had a 32% increased heart disease risk compared with those who are not overweight. Obesity increased risk 81% compared with those women with normal weight. There was a 16% heart disease risk increase for every five-unit increment in BMI (79). In overweight individuals this risk, independent of hypertension and hypercholesterolemia, may be related to low-grade inflammation, alterations in coagulation, and blood vessel function. During a weight loss intervention (i.e., using a meal replacement and fat-reduced diet) metabolic changes occurred in premenopausal versus postmenopausal women. The BMI, fat mass, waist circumference, systolic BP, and triglyceride, glucose, leptin, and cortisol levels were higher in postmenopausal women at baseline. Both groups achieved substantial and comparable weight loss, which was exclusively due to fat mass reduction in postmenopausal women compared with lean body mass reduction in premenopausal women (21% of weight loss). Total cholesterol and LDL cholesterol levels were significantly lowered in both groups, whereas BP, triglycerides, HDL cholesterol, and glucose levels significantly improved only in postmenopausal women (80). Therefore, weight loss in postmenopausal women reduced METS prevalence through the improvement of metabolic risk factors.

Body weight increase during a woman’s midlife has also been approached by exercise programs. Twice weekly strength training has been found to prevent intra-abdominal fat increase in postmenopausal women (81). Postmenopausal women who were previously sedentary, overweight, or obese experienced a graded dose–response change in fitness across levels of exercise training, without significant changes in systolic or diastolic BP values from baseline to 6 months later (82). If these measures fail, pharmacologic intervention can be considered with drugs such as sibutramine and orlistat. Sibutramine induces weight loss (5% in 3 months) and reduces CVR in obese subjects (30–40 kg/m²). Gastrointestinal surgery may be considered for women with severe obesity (BMI ≥40) or those with BMI ≥35 and co-morbidities.

**Metabolic Syndrome**

There are a number of definitions for the METS. The third expert panel in Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) established diagnostic criteria for this syndrome when three or more of the following factors are present: abdominal obesity, blood triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL, systolic BP ≥130 or diastolic BP ≥85 mm Hg, and a basal glycemia ≥110 mg/dL (83). The International Diabetes Federation has defined the METS using similar criteria, although cutoff values for abdominal circumference and basal glycemia are different (Table 2) (84). Therefore, METS prevalence changes according to the classification used, modifying mortality rate and other statistics. The prevalence of a Framingham risk score ≥10% is higher in women with bilateral oophorectomy before 50 years (22%) compared with matched controls with intact genitals (15%), suggesting that these women may be at higher risk for type 2 diabetes and CVD compared with the general population (85). However, in young individuals (<50 years) with severe coronary disease the Framingham risk score has limitations. For example, after a myocardial infarction 75% would not have qualified to receive pharmacologic therapy to reduce cholesterol levels (86).

In Spain, METS prevalence in the general population is about 13.6%. Logistic regression analysis showed that hypertension and diabetes, components of the METS, increased CVD (87). In the Italian Ventimiglia di Sicilia study, which includes individuals aged 35–75 years followed for 15 years, the METS was significantly more prevalent in women (31.5%) than in men (12.4%), and the survival curve of METS subjects was not influenced by fasting glucose (88). The longitudinal Study of Women’s Health Across the Nation (SWAN) has demonstrated that the incidence of METS increased progressively from 6 years before to 6 years after the menopause onset, independent of aging and other known CVD risk factors. The increase is steeper during the menopausal transition compared with the postmenopausal years (89). It has been long thought that progressive estrogenic loss was the cause. However, changes in E levels are weak and a nonsignificant predictor of METS risk. Insulin resistance is associated with deleterious health outcomes, such as type 2 diabetes and CVD. Using data from the National Health and Nutrition Examination Survey (NHANES II) mortality follow-up, the prevalence and the relative risk (RR) of cardiovascular death for individuals with METS...
components were determined in the overall population and across ethnic groups (90). The adjusted RR for cardiovascular death was highest with diabetes, elevated BP, and high triglycerides. Although in cardiovascular death RR differs significantly for some of the different components, the overall findings were similar across ethnic groups. The METS subjects had significantly higher CPR and lower adiponectin levels compared with control subjects. The METS is driven largely by obesity in relation to insulin resistance, both being frequent abnormalities that increase CVR in postmenopausal women. The BMI correlated strongly with markers of insulin resistance, as well as as adipocytokine values. After controlling for BMI, only leptin was predictive for the METS (91). Obesity increases menopausal symptom severity and quality of life (92, 93), factors already described that increase CVR among hypertensive subjects (67).

Because the METS can contribute to accelerated atherosclerosis and cardiovascular events, educational programs may be a way of preventing METS complications, especially among young postmenopausal women. Postmenopausal women previously diagnosed with METS after participating in an educational program significantly improved their knowledge regarding the menopause and related issues, and their awareness of related risks. These cost-effective measures could eventually reduce cardiovascular morbidity and mortality among high-risk populations (94).

The METS treatment consists basically in improving lifestyle, increasing physical activity at least four times a week for 30 minutes, and reducing caloric ingestion (carbohydrates and saturated fat). In cases of insulin resistance (homeostasis model assessment > 2.5), slow release metformin can be added at 1,000 mg/day. Regular physical activity across lifespan may prevent or delay METS onset (95). In a randomized study, postmenopausal women were assigned to 12 months of aerobic exercise 5 days/week or to a stretching control group. Women who followed the exercise program had a 4% decrease and controls, a 12% increase in circulating insulin, whereas the leptin levels decreased among exercisers, remaining constant among controls (96). Recent research suggests that traditional mind–body practices, such as yoga and tai chi, may offer safe and cost-effective strategies for reducing insulin resistance syndrome-related risk factors for CVD in older populations, including postmenopausal women (97). In cases of hypertriglyceridemia and METS, fenofibrate may improve fasting and postprandial free fatty acid oxidation and inflammatory responses, which correlate to reductions in very low-density lipoprotein particles (98).

CO-MORBID CONDITIONS THAT MAY INCREASE FEMALE CARDIOVASCULAR RISK

In recent years different clinical co-morbid conditions have been identified to increase CVR in climacteric women and these need to be properly evaluated. Many of these co-morbid conditions are quite frequent among perimenopausal women and act synergistically, creating a vicious circle from which exiting becomes difficult. Because HT is no longer the panacea for climacteric management (perhaps due to more risks than benefits) proper identification and treatment of these co-morbid conditions are imperative.

Sleeping Disorders

Women report more sleeping disorders throughout their lifetime than do men. The prevalence of sleeping difficulty increases as women transition from the premenopausal to the postmenopausal period. Sleeping architecture is associated with the neuroendocrinology of the menstrual cycle, body temperature regulation, and hot flashes. At the same time, hot flashes and other vasomotor symp-
toms that influence sleep continue years beyond the menopause (99–101). Sleeping difficulties, especially problems related to falling asleep, are distressing during the menopausal transition and postmenopausal years. They may contribute to increase female CVR. Some 16% of postmenopausal women report having difficulty in falling asleep and 41% report waking up frequently during the night (102). Women in midlife with higher levels of marital happiness have a lower risk for sleeping complaints, less difficulty falling and staying asleep, or early morning awakenings (103).

In midlife adults, classified in four groups according to sleep duration, the METS incidence and its components increased in both short and long sleepers compared with those sleeping 7–8 hours by night. Correlation between sleep duration was found with abdominal obesity, elevated fasting glucose, and hypertriglyceridemia (104). In women, there is also a stronger association between poor sleeping quality and coronary heart disease, type 2 diabetes, and hypertension (105, 106). In addition, modest associations between short sleeping duration and difficulties of maintaining sleep and incident myocardial infarction were seen in middle-aged women but in men from the general population (107). These gender differences are associated with greater psychosocial distress and higher fasting insulin, fibrinogen, and inflammatory biomarker levels, but only for women (108). Deep sleep or slow-wave sleep interruption reduces physical well-being and is related with glucose metabolic alterations. Insulin resistance is facilitated when individuals are roused just when they are about to fall into deep sleep, independent of the total sleep duration. The body’s inability to recognize normal insulin levels leads to hyperglycemia, body weight elevation, and eventually type 2 diabetes (109). Strategies to ameliorate sleep quality should be considered as a potential intervention aimed at reducing or delaying the development of type 2 diabetes, and indirectly, CVR.

Recent data analysis of the WHI study included known risk factors that might confound any apparent association between sleep duration and ischemic stroke. The increased RRs for stroke compared with the 7-hour sleep group was 14% for 6 hours or less sleep, 24% for 8 hours of sleep; and 70% for 9 or more hours of sleep. Thus, sleeping 9 hours or more per night significantly increases the risk for ischemic stroke among postmenopausal women, whereas sleeping less than 6 hours showed a modest increase in risk, but was reported by twice as many women (110). The increased risk for ischemic stroke associated with short and long sleep among postmenopausal women could not be completely explained by medical, psychological, and lifestyle variables. The investigators did not directly associate long sleep and ischemic stroke, as this may be due to some unmeasured factors, including other undiagnosed sleeping disorders. In addition, discordant results between sleep observational studies and the WHI cohort may be related to age and methodological considerations, including overlapping depressive and menopause-related complaints, psychosocial factors, and age-related CVR prevalence.

According to a recent publication of the Coronary Artery Risk Development in Young Adults (CARDIA) study, an ongoing project including healthy volunteers, sleep duration also influences the development of coronary artery calcification (111). Individuals were submitted to two electron-beam CT scans to assess the buildup of coronary artery calcification in a 5-year interval. Subjects also filled out sleep questionnaires, kept a log of their hours in bed, and participated in six nights of sleep studies in the 5 years. Coronary artery calcification was 12% during the 5-year follow-up, 27% in those who slept less than 5 hours compared with 11% in those sleeping 5–7 hours and 6% in those sleeping more than 7 hours per night. The benefit of 1 hour of additional sleep produced a comparable effect to that obtained by lowering systolic BP by 16.5 mm Hg. In addition, sleep benefits are
greater for women. It seems reasonable, despite the limited available evidence, to recommend sleep quality improvement among climacteric women, especially among those referred for these problems.

Some of the sleeping problems that women typically attribute to hot flashes may be caused instead by primary sleeping breathing disorders. These include breathing frequency or depth abnormalities while asleep, the most common being the obstructive apnea/hypopnea syndrome, which is an independent risk factor for hypertension, is associated to cardiovascular dysfunction, increases METS prevalence, and exacerbates atherosclerosis (112). It affects some 2%–4% of the adult population and is associated with elevated body weight. The treatment for obstructive apnea/hypopnea syndrome with continuous positive airway pressure lowers BP, reduces heart arrhythmia frequency, and improves endovascular inflammation marker levels (113).

Another sleep-related condition that has been associated to CVD is the restless legs syndrome (114). It is a disorder characterized by restlessness and a need to move the legs, mainly at night, which starts or worsens during rest. The condition affects 5%–10% of the adult population and is two times more prevalent in women. Patients face twice the risk of stroke and heart disease compared with unaffected individuals. Patients with restless legs syndrome may repeatedly awake during the night and, as with individuals with other sleeping disorders, many experience daytime fatigue, impaired memory, and concentration problems. The BP increase is sleep-related to periodic leg movement. The influence of sleep on anterior pituitary hormone pulsatile secretion and sleep cycles has been reported several decades ago (98–100). It is plausible that hormone secretion alterations may be involved in the mechanism that increases CVR in patients with restless legs syndrome. In fact, Oertel et al. (115) have obtained good results treating restless legs syndrome with the dopamine agonist carbergeline, as evaluated by polysomnography.

Sleep plays a vital role in promoting a woman’s health and well-being. Women face other co-morbid conditions, such as depression and psychological stress that disturb their sleeping and resting habits. During normal sleep, growth hormone and PRL are released and cortisol secretion is reduced. Furthermore, low quality and quantity of sleep alters the central appetite control and hormones, such as leptin and ghrelin, which are involved in obesity genesis and hence CVR (116). Estrogen therapy improves sleep, quality of falling asleep, and decreases night restlessness and awakenings in both symptomatic climacteric (vasomotor symptoms) and nonsymptomatic postmenopausal women (117). Exercise intervention may improve sleep quality in sedentary, overweight, and postmenopausal women. Thus, increased fitness is associated with improvements in sleep (118). Without the need of medication, moderate aerobic exercise can improve sleep quality among patients with insomnia and reduce their anxiety state. Phytotherapy may also help improve quality of life related to sleeping disorders and hot flashes (119, 120), and thus improve quality of life and reduce CVR.

**Depression**

Health risks associated to depression seem to be more critical for women. Depression is common among climacteric and older women, although it may have a long course and evolution, starting from fertile age. In a survey covering more than 6,000 individuals aged 17–39 years, women were more prone than men in experiencing an episode of depression, and those who had at least one episode were more likely to have the METS (121). The association between depression and hypertension is especially strong. Depression in men is not associated with the METS or its components. In a female cohort followed for 15 years, those who had frequent and intense anger, were tense, or stressed also had an increased risk of developing the METS (122). Depression has been associated to other CVR factors such as insulin resistance, hypertension, smoking, alcohol abuse, and sedentarism. In a study of more than 900 patients with coronary heart disease, those with both type 2 diabetes and depressive symptoms were more likely to die than heart patients without these conditions, suggesting a synergistic effect (123).

The WHI study provided data regarding the association between depression and CVR in women followed for an average of 4.1 years (124). Current depressive symptoms were reported by 15.8% of postmenopausal women, and was significantly associated to CVR. In addition, antidepressive treatment did not reduce depression-associated risks. Type 2 diabetes and depression often go hand in hand, although it is unclear which condition develops first in patients who finally develop both entities. Considering data from the Multi-Ethnic Study of Atherosclerosis (MESA), which examined risk factors for atherosclerosis in an ethnically diverse group of individuals between ages 45 and 84 years, Golden et al. (125) suggest that the answer is dual, as patients with depression have an increased risk of having type 2 diabetes and vice versa, patients with type 2 diabetes have increased risk for depression. After considering confounding factors, such as overweight, sedentarism, and smoking, the risk of developing diabetes was 34% higher for those with depressive symptoms. When individuals with increased depressive symptoms at the initial visit were excluded, those who had high fasting glucose levels by the end of the study were 54% more likely to present with depressive symptoms than those without diabetes.

Cardiac deaths after depression increase whether or not subjects already have heart disease. A 54-month observational multicenter Dutch study including 2,900 participants reported that heart disease deaths were nearly fourfold among participants with major depression who did not have heart disease at the beginning of the study. This figure was threefold for those already having heart disease at study initiation. Individuals with minor depression also had an increased risk of dying of heart disease both among those with and without pre-existing heart disease. The prevention and treatment of depression may be a relevant intervention to reduce fatal cardiac events. The explanations for these findings include that depression may impair platelets in blood and decrease heart rate variability. Unhealthy cortisol levels may also activate the immune system and decrease insulin resistance, all which increase heart disease risk (126).

**Stress and Psychosocial Factors**

Certain behaviors, psychological stress, and affective problems (that increase stress) are associated with ovarian dysfunction and reduced E levels, placing certain young women on a high-risk course for heart disease. Stress has an essential role in the development and exacerbation of mood problems. It intensifies somatic menopausal symptoms, increasing the risk of mood disorders throughout life and specifically in the menopausal transition (127). Chronic stress also affects the hypothalamic-pituitary and ovarian axis and proinflammatory cytokine secretion, hence increasing CVR. Clarkson’s experimental studies in monkeys suggest that stress can actually reduce E levels during the reproductive years, much earlier in life and hasten CVR development. When combined HT was delayed (the equivalent of 6 years in women) there was no benefit or may even hasten CVR development. When combined HT was delayed (the equivalent of 6 years in women) there was no benefit or may even accelerate disease progress if atherosclerosis was already initiated. The interaction of premenopausal social status and oral contraceptive (OC) exposure significantly predict postmenopausal coronary artery atherosclerosis. Thus, subordinate animals not receiving
OCs developed coronary atherosclerosis twice as often as similarly untreated dominants, suggesting that social relationship may influence vascular health (128, 129). It is admitted that ovarian hormones protect premenopausal women from CVD and that endogenous E reduction accelerates CVD. Thus, premenopausal women with angiographically confirmed coronary disease have significantly lower plasma E2 than controls (130). The Women’s Ischemia Syndrome Evaluation (WISE) study assessed female ischemic heart disease pathophysiology and how sex hormones and other gender-specific findings influence clinical aspects of the disease. In this study, women referred for angiograms due to chest pain and suspected ischemia were enrolled to assess their frustration, increased aggression and anger (131). Although anger and hostility are not predictive of coronary artery disease in women, those who express anger may be at increased risk if they also have other risk factors such as age, history of diabetes, and elevated serum lipid levels.

The association between psychological risk factors for CVD, endothelial function, and HT use has been prospectively studied among premenopausal women (13 years earlier), and later at the postmenopausal follow-up when an ultrasound evaluation was carried out. Women with anxiety/depression in the premenopausal years presented significantly less vasodilation at follow-up evaluation. Non-HT-using postmenopausal women with anger scores at follow-up were also associated with significantly less vasodilatation (132). This study supports an association between psychosocial risk factors for CVD and impaired brachial artery dilatation in postmenopausal women, which may be masked by HT.

Individuals who suffer from job burnout syndrome were nearly twice as likely to develop type 2 diabetes, whereas when the possible effect of BP was corrected, the risk was fourfold (133). Unhealthy jobs and stressful social relations may contribute to indirect metabolic alterations that increase CVR. The burnout syndrome has also been associated with an increased risk of CVD, as it may favor a low-grade systemic inflammatory state that contributes to atherosclerosis (134). Higher levels of burnout symptoms were associated with higher TNF-α and lower IL-4 levels, suggesting a state of systemic inflammation that may explain their reported increased CVR.

Individuals with panic disorders are more likely to be female, smokers, have a history of depression, and elevated body weight. Panic episodes often show symptoms similar to those of heart attacks. They may suffer similar endocrine and hematologic changes reported in depression, which may favor CVR (135).

Menopausal women and their familial, social, and labor position may have negative effects on CVR. Strategies intended to optimize the assessment and treatment of symptomatic perimenopausal women taking into account stressful life events and co-morbid mood disorders should be considered as a potential intervention to prevent or delay the development of CVD.

**Vitamin D Insufficiency**

Both basic science and clinical studies support the protective role of vitamin D on cardiovascular health, although there are controversial results. Hypovitaminosis D is associated with disturbed glucose metabolism and pancreatic cell dysfunction, lipoprotein alterations, hypertension, overweight, and obesity. Vitamin D is sequestered in the large adipose mass of obese and overweight individuals. Obese individuals may have low self esteem regarding their body and hence minimize sunlight exposure (136, 137). Low vitamin D levels are frequent in healthy postmenopausal women (138, 139). In healthy men and women studies from several ethnic groups, hypovitaminosis D has been associated not only with lowered insulin secretion and sensitivity, but also with adverse effects on both total cholesterol and LDL cholesterol concentrations (140, 141). Plasma vitamin D levels are inversely associated to incident hypertension risk, independent of age, BMI, physical activity, race, menopausal status, and other variables (142). At the same time there is evidence demonstrating an association between depression status, and its severity, with decreased vitamin D levels (143). Thus, a triangle is formed by low vitamin D levels, depression, and CVR.

Follow-up of a cohort of 13,000 initially healthy individuals of the National Health and Nutrition Examination Survey (NHANES III) showed that low vitamin D levels led to a 26% increased death risk (144). Nearly 700 died from some form of heart disease, with 400 of these being vitamin D deficient. Although the results were not significant, the investigators proposed vitamin D deficiency as a distinct and separate risk factor for CVD death aside from the well-known risk factors. A previous publication from the same researchers showed an 80% increased risk of peripheral artery disease related to vitamin D deficiency (145). Thus, among individuals with the highest vitamin D levels (>29.2 ng/mL) only 3.7% had peripheral artery disease compared with 8.1% among those with the lowest levels (<17.8 ng/mL). However, a causal relationship remains to be demonstrated.

Postmenopausal women from the WHI cohort were randomly assigned to receive daily 1,000 mg of calcium plus 400 IU of vitamin D (18,176 women) or placebo (18,106 women), and followed each year for 7 years (198). At the end of follow-up (7 years) calcium and vitamin D supplementation did not reduce the risk of developing diabetes among postmenopausal women (146). Nevertheless, the WHI publication did not give information regarding leisure activities and sun exposure, and some women from the placebo group used supplements that might have attenuated the placebo effect compared with the active group (147). In addition, the recommended vitamin D dosage for this study may not be sufficient to maintain normal blood levels. Finally, no serum vitamin D determinations were performed during the WHI study. Vitamin D improvement may have an additional value to maintain cardiovascular health in the general population. Despite this, optimal vitamin D dose remains to be determined and due to the complexity of CVD, correction of low vitamin D levels per se does not guarantee its prevention.

**Rheumatoid Arthritis**

Inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosus, are associated to increased cardiovascular events. This is independent of traditional cardiac risk factors and when disease is controlled. Rheumatoid arthritis is a multifactorial disease in which both environmental and genetic factors play a role, being two to three times more frequent in women than in men and strongly associated with sex hormones (148). It has been postulated that genes in sex chromosomes may be responsible for the higher female prevalence. In the postpartum period, rheumatoid arthritis frequently develops or flares, especially if women breastfeed. Most women with rheumatoid arthritis have remission during pregnancy and hormone contraception due to hormone and cytokine changes (149). Menopausal transition is a peak time for rheumatoid arthritis initiation, which reinforces links between steroid hormones and immunity. Adrenal androgen levels are reduced among women with premenopausal rheumatoid arthritis onset, which are even reduced several years before clinical initiation (150).

Patients with rheumatoid arthritis have reduced life expectancy and excess CVD mortality compared with the general population. The CVD and rheumatoid arthritis common pathway is complex and has been related to dyslipidemia, increased homocysteine,
impaired insulin sensitivity, and endothelial dysfunction. Anti-inflammatory markers seem to be lower in both rheumatoid arthritis and atherosclerosis patients when compared with controls (151). Professionals involved in climacteric care should provide appropriate evaluation in an individualized and active manner because there seems to be a link. Individuals with rheumatoid arthritis have a higher risk of developing heart disease than the general population; however, it is difficult to identify which patients are at increased risk. A major medical challenge is the detection and prevention of heart disease in patients with rheumatoid arthritis who show no symptoms of heart disease.

FINAL REMARKS

Premenopausal women have a lower risk for cardiovascular events and mortality than men. This fact suggests that endogenous Es, such as E2, protect the cardiovascular system during fertile years. Several observational studies and a few small clinical studies conducted in healthy younger postmenopausal women support this hypothesis. Since the publication of the WHI study, patients and physicians have changed their attitude toward HT use due to increased risks and the lack of benefit on the cardiovascular system, limiting HT prescription to vasomotor symptoms and vaginal atrophy for a limited time. Risks outweigh the benefits of fewer hip fractures. However, randomized controlled trials with clinical end points have shown that previously held data may not be accurate. Long-term mortality is significantly higher in women subject to bilateral oophorectomy before the age of 45 years, especially among those who did not receive E (152). In addition, an increased death risk associated to CVD, after excluding cerebrovascular disease, has been recently reported in women with bilateral oophorectomy before age 45 years (153), confirming Clarkson’s hypothesis—developed in monkey studies—regarding premenopausal E’s cardiovascular system protection (128, 129). The existence of a ”window time,” close to the menopause onset, for HT initiation has been proposed, which has been indirectly supported by most of the published observational studies. This contrasts to the WHI population in which women were randomized to HT long after the onset of menopause. Some 80% of women in the Nurses’ Health Study initiated HT in the early years of the menopause (58), whereas WHI women had a mean baseline age of 63 years. The mean woman age difference between the two studies was more than a decade. However, it remains to be demonstrated whether HT given earlier would confer protection many years later at a time when CVD prevalence is high. Furthermore, we have to place in scene all health aspects, including impaired insulin sensitivity, and endothelial dysfunction. Anti-inflammatory markers seem to be lower in both rheumatoid arthritis and atherosclerosis patients when compared with controls (151). Professionals involved in climacteric care should provide appropriate evaluation in an individualized and active manner because there seems to be a link. Individuals with rheumatoid arthritis have a higher risk of developing heart disease than the general population; however, it is difficult to identify which patients are at increased risk. A major medical challenge is the detection and prevention of heart disease in patients with rheumatoid arthritis who show no symptoms of heart disease.

FIGURE 1

The menopause transition is associated with a decline in ovarian steroid secretion and very frequently with a progressive increase in body weight that is likely related to fat mass as an endocrine organ. The increase in fat mass (visceral fat) produces an increase in free fatty acids (FFA), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), leptin, and resistin, and reduces the adiponectin secretion. Low ovarian steroid secretion increases endothelial dysfunction, inflammatory reactions, oxidative stress, and alters blood lipid levels. Low vitamin D levels and E2, and increased body fat central mass contribute to insulin resistance, the metabolic syndrome, hypertension, and atherosclerosis. A number of co-morbid conditions are also very frequent, including sleep disorders, depression, stress and psychological factors, vitamin D insufficiency, sexual dysfunction, and rheumatoid arthritis, that contribute to alter the neuroendocrine system and the immune system, which at the same time aggravate the health status. Biopsychological and social health equilibrium is the key to reduce cardiovascular risk. Menopause is not the only cause of all of these derangements, although low estrogen levels may exacerbate symptoms and complaints. The algebraic sum (the final result) is a significant increase in cardiovascular risk. LDL-C = low-density lipoprotein cholesterol.
co-morbidity and those individual factors that may increase CVR independent of women’s menstrual status. We have enumerated new co-morbid factors—several affecting women even before the menopause—that require appropriate diagnosis and treatment other than HT. In addition, perimenopausal metabolic changes seen in longitudinal studies are reminiscent of the METS (154). Hence, metabolic adipose tissue and liver-related hormones create a new equilibrium (9), difficult to be corrected by HT.

The results of the WHI cohort have been a source of controversy, not only concerning HT, as data also affect vitamin D supplements, sleep disorders, and other topics concerning postmenopausal women’s health. The WHI trial has many methodological flaws and biases that have been criticized in the past years. However, other published studies, as already discussed, confirm increased CVR. At present, HT should be restricted to treat menopausal symptoms and for a limited time. The indications for menopausal prevalent chronic conditions are not justified based on the dictum Primum non nocere. Health deteriorates with aging and the menopause creates specific gender characteristics. The CVR involves many factors and conditions that need a wide open interpretation. For many years gonadal steroid treatments have been considered, perhaps exaggeratedly, the panacea for menopause-related symptoms, complaints, and prevalent diseases. However, there is no such panacea because life and menopausal metabolic adjustments are very complex. During the menopausal transition nearly all women gain body weight. Obesity, a component of the METS, comprehends the axis around which all the other factors revolve and not only increases CVR but also deteriorates quality of life, therefore its assessment among menopausal women should be of major relevance. Adipose tissue may be considered as an endocrine organ. Abdominal obesity alters serum free fatty acid levels, decreasing adiponectin while increasing leptin, TNF-α, IL-6, resistin, and secretion (Fig. 1). These changes increase insulin resistance and METS risk. Vulnerable times for weight gain during a woman’s life cycle include early adulthood, the childbearing years, and the menopause. Thus, a healthy diet and exercise behaviors must be particularly emphasized during these years.

The Atherosclerosis Risk in Communities Study (ARIC), carried out to investigate the origin and progression of various atherosclerotic diseases (155), proposed four healthy measures to reduce CVR and death rate in individuals aged 45–64 years: [1] eating at least five fruits and vegetables daily, [2] exercising at least 2.5 hours per week, [3] maintaining BMI between 18.5 and 30 kg/m², and [4] not smoking. Following these recommendations, compared with people with less healthy lifestyles, reduced CVD and mortality incidence 35% and 40%, respectively. Benefits were obtained despite a relatively modest change in health habits. In addition, a healthy lifestyle was beneficial when compared with all individuals with three or fewer healthy habits. Individuals adopting only three healthy habits experienced lower mortality but not fewer CVD events during the same period. Scientific societies have released CVD prevention guidelines that are useful tools for the management of postmenopausal women (156, 157).

Professionals engaged in women’s healthcare should encourage healthy lifestyles, increased physical activity, and quitting harmful habits (i.e., tobacco and alcohol), which are very useful cost-effective ways of decreasing CVR in both developing and industrialized countries (158). Equally, medical colleges should encourage health authorities to include the METS and educational programs for high risk female populations as part of primary care services, seeking to increase their knowledge regarding the effects of the menopause on health and CVR. Finally, individual’s feelings and desires during the menopausal transition and postmenopausal years are influenced by culture and social factors that are not expected to be easily changed. Each condition, symptom, and complaint deserves evaluation and consideration to fulfill women’s expectations.

Although a lot of scientific information has been gathered regarding general health and co-morbidities, we have completed a full circle and still we stand nearly in the same place as Naftolin et al. (1) stated 5 years ago. More studies are required to continue learning about the menopause and hence improve health care among aging women. Future prospective studies should include new tools intended to assess relevant co-morbidities and hence provide more focused interventions.

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