Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone

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ABSTRACT
Most available postmenopausal hormone replacement therapies (HRT) offer similar efficacy, but differ with respect to the cardiovascular risks associated with their use. There is a wealth of evidence to suggest that, unlike oral estrogens, transdermal estradiol does not increase the risk of venous thromboembolism, probably due to its lack of effect on the coagulation cascade, including thrombin generation and resistance to activated protein C, and does not increase the risk of stroke. It is cardioprotective, significantly reducing the incidence of myocardial infarction compared with non-users; it significantly reduces the incidence of new-onset diabetes, a risk factor for myocardial infarction. Micronized progesterone has also been shown not to increase the risk of venous thromboembolism and further reduced the incidence of new-onset diabetes when combined with transdermal estrogen. Micronized progesterone has a neutral effect on the vasculature, including a neutral or beneficial effect on blood pressure. Therefore, experimental and clinical data indicate that transdermal estradiol and micronized progesterone could represent the optimal HRT, particularly in women at risk of adverse events.

INTRODUCTION
Most available postmenopausal hormone replacement therapies (HRT) are approved for the relief of climacteric symptoms and generally offer similar efficacy1. However, HRT preparations differ with respect to the risks associated with their use, particularly cardiovascular risks.

EVIDENCE-BASED MEDICINE IN HRT

The benefits and risks associated with HRT have been investigated in only one randomized, double-blind, placebo-controlled study – the Women’s Health Initiative (WHI) study2,3. In this two-arm study, 27000 postmenopausal women received HRT or placebo; in one arm, women who had not had a hysterectomy (n = 16608) received oral conjugated equine estrogens (CEE, 0.625 mg/day) plus medroxyprogesterone acetate (MPA, 2.5 mg/day) or placebo and, in the second arm, women who had undergone a hysterectomy (n = 10739) received unopposed CEE (0.625 mg/day) or placebo. Four major safety concerns were associated with the use of oral HRT in this study2,3: venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, myocardial infarction (MI), stroke, and breast cancer (for information on HRT and breast cancer, see the paper by Gompel4 in this Supplement). However, only one HRT regimen was studied, and thus the results cannot be applied across all HRT regimens; furthermore, the clinical trial conditions did not accurately reflect clinical practice. For example, the mean age of women in both arms of this study was 63 years, and they had more risk factors than are generally seen in women of this age5.
Although studies such as the WHI represent the gold standard in terms of evidence-based medicine, the definition of evidence-based medicine is not restricted to randomized, controlled clinical trials. Evidence-based medicine should consider the total body of evidence in order to optimize therapy for each individual, including large, case-controlled and cohort studies, experimental data that explain biological plausibility, and clinical expertise, which, in the case of HRT, is the practical experience of gynecologists. Although no randomized, controlled clinical trials have been conducted investigating the benefits and risks associated with transdermal estrogen and oral micronized progesterone, a wealth of data contribute to the total body of evidence supporting their use.

VENOUS THROMBOEMBOLISM

In the WHI study, unopposed estrogens (CEE) were associated with a 33% increased risk of VTE (hazard ratio (HR) 1.33; adjusted 95% confidence interval (CI) 0.86–2.08), with a more than two-fold increase in the risk of VTE with continuous combined HRT (HR 2.11; adjusted 95% CI 1.26–3.55), compared with non-users. Indeed, the addition of MPA increased the risk of VTE by a further 59% compared with CEE alone (ratio CEE/CEE + MPA, HR 1.59; adjusted 95% CI 0.37–0.94; p = 0.03). 7

Estrogens and venous thromboembolism

There is a wealth of experimental evidence demonstrating that oral estrogens activate the coagulation cascade, increasing thrombotic risk, while transdermal estradiol does not. 8–13 Various explanations for the different effects of oral and transdermal estrogens on the coagulation cascade have been proposed. Thrombin generation, a marker of the prothrombotic state and therefore thrombotic risk, is increased in women receiving oral estrogens, probably due to the hepatic first-pass metabolism of estrone, the main metabolite of oral estradiol formed in the intestine and liver. 8 The lack of effect of transdermal HRT on thrombin generation, and thus thrombotic risk, could therefore be associated with the avoidance of this metabolic route via transdermal administration.

Resistance to activated protein C (APCr), a key component of the coagulation cascade, is a common risk factor for VTE. 14 APCr has been consistently shown to be more significantly increased in women receiving oral estrogens compared with transdermal estradiol. 9–11 Mutations in factor V (factor V Leiden) are often associated with APCr, with heterozygous mutations carrying a seven-fold increased risk of VTE, and homozygous mutations carrying an 80-fold increased risk. 15,16 Reduced sensitivity to APC and increased thrombotic risk have also been shown in women without factor V Leiden. 17 The increase in APCr in response to oral estrogens and, importantly, the lack of effect of transdermal estradiol on APCr, occur both in the presence and absence of heterozygous factor V Leiden mutations. 9–11 Combining oral micronized progesterone with transdermal estradiol does not increase APCr; 8,18 however, combination with norpregnane derivatives can increase APCr. 18

Three large, case-control or cohort studies in unselected populations also support the significantly increased risk of VTE associated with oral estrogen therapy, but not with transdermal estradiol. Available evidence indicates that oral estrogens also increase the risk of VTE in women receiving transdermal estradiol compared with non-users (odds ratio (OR) 2.5; 95% CI 1.9–3.4), while the risk of VTE in women receiving transdermal estradiol was not significantly increased (OR 1.2; 95% CI 0.9–1.7), compared with non-users. 22

Transdermal estradiol has also been shown not to increase the risk of VTE in women who are at high risk, such as those with prothrombotic mutations (including factor V Leiden), overweight/obese women, and those with a history of VTE. 23–25 In women with prothrombotic mutations enrolled in the case-control ESTHER study, the risk of VTE was similar in those receiving transdermal estradiol and non-users (OR 4.4; 95% CI 2.0–9.9 and OR 4.1; 95% CI 2.3–7.4, respectively). 23 However, oral estrogens were
associated with a 25-fold increased risk of VTE in women with prothrombotic mutations, compared with non-users without mutations (95% CI 6.9–95.0).

Obesity is currently a major public health problem, highlighted by the facts that 35% of women enrolled in the combined HRT arm of the WHI study were overweight and a further 34% were obese. Being overweight is a risk factor for VTE: in women aged 45–70 years, being overweight (25 kg/m² < body mass index (BMI) ≤ 30 kg/m²) or obese (BMI > 30 kg/m²) was associated with 2.5- and 3.9-fold increases in the risk of VTE, respectively, compared with women of normal weight (BMI ≤ 25 kg/m²)24. In the ESTHER study, the use of oral estrogens was associated with a 10-fold increase in the risk of VTE in overweight women (OR 10.2; 95% CI 3.5–30.2) and a 21-fold increase in the risk of VTE in obese women (OR 20.6; 95% CI 4.8–88.1)24. In contrast, in women with an increased BMI, the use of transdermal estradiol was associated with a similar VTE risk as in non-users (overweight: OR 2.9; 95% CI 1.5–5.8 and OR 2.7; 95% CI 1.7–4.5, respectively; obese: OR 5.4; 95% CI 2.1–14.1 and OR 4.0; 95% CI 2.1–7.8, respectively).

Women who have previously had VTE are at increased risk of a recurrent event. In the Menopause, Estrogen, and Veins (MEVE) cohort study involving 1023 postmenopausal women with confirmed first VTE, transdermal estradiol did not increase the risk of recurrent VTE (HR 1.0; 95% CI 0.4–2.4), while oral estradiol did (HR 6.4; 95% CI 1.5–27.3), compared with non-users25. The lack of effect on transdermal estradiol on the risk of recurrent VTE was consistent across all subgroups studied.

Progestogens and venous thromboembolism

Progestogens can further increase the risk of VTE, as demonstrated in the WHI study; the addition of MPA to CEE doubled the risk of VTE compared with women receiving placebo3. However, the progestogen effect on VTE risk is dependent on the progestogen used. In the ESTHER case-control study, the use of oral micronized progesterone or pregnane derivatives was not associated with an increased thrombotic risk, compared with non-users (OR 0.7; 95% CI 0.3–1.9 and OR 0.9; 95% CI 0.4–2.3)26. However, the use of norpregnane progestogens was associated with a four-fold increase in the risk of VTE compared with non-users (OR 3.9; 95% CI 1.5–10.0). A similar pattern was also seen in the MEVE study which investigated recurrent VTE25, and in the E3N study in which the thrombotic risk significantly differed by concomitant progestogen type (homogeneity; p < 0.01); micronized progesterone did not increase the risk of VTE, while norpregnane progestogens did, compared with non-users20.

MYOCARDIAL INFARCTION

Estrogens have a cardioprotective effect in women, as demonstrated by epidemiological and experimental data and biologic plausibility27. However, in the WHI study, oral unopposed estrogens (CEE) had no effect on the overall risk of coronary heart disease (CHD), comprising acute MI requiring hospitalization, silent MI determined by serial electrocardiograms and coronary death (HR 0.91; 95% CI 0.75–1.12 vs. placebo)3. In younger women aged 50–59 years, there was a trend towards a reduction in CHD risk (HR 0.56; 95% CI 0.30–1.03) in the WHI study. The use of combined HRT (CEE + MPA) significantly increased the risk of CHD (HR 1.29; 95% CI 1.02–1.63), mainly due to an increase in non-fatal MI, indicating the crucial contribution of progestogens to arterial risk. These results reflect data from the Clarkson group involving female cynomolgus monkeys in whom menopause was induced by ovariectomy28,29. Estradiol and CEE demonstrated a cardioprotective effect, significantly reducing coronary atherosclerotic plaque size compared with controls28,29. The addition of MPA negated the cardioprotective effect of CEE28. However, the addition of progesterone had no significant effect on the cardioprotective effect of estradiol29. Therefore, the type of progestogen is important, as different progestogens appear to have different cardiovascular effects20.

Studies in human endothelial cells further demonstrate the different effects of different progestogens31. Natural progesterone and dihydroprogesterone, the stable metabolite of dydrogesterone, increased the synthesis of nitric oxide (NO), a vasodilatory and anti-inflammatory molecule vital for vascular function, and increased the expression and activity of endothelial NO synthase (eNOS) in human endothelial cells. MPA and dydrogesterone did not affect NO synthesis. Estradiol was also associated with a strong induction of NO synthesis and eNOS activity. When co-administered with estradiol, natural progesterone, dydrogesterone, and its metabolite did not affect the induction of NO synthesis associated with estrogen, but MPA significantly reduced this effect (p < 0.05)31. Transdermal estradiol also appears to have a cardioprotective effect, as demonstrated by data from almost 700 000 women in the Scandinavian National Register32. The relative risk (RR) of MI was reduced significantly in women receiving unopposed transdermal estradiol compared with non-users (adjusted RR 0.62; 95% CI 0.41–0.93), while oral estradiol had no effect on the rate of MI (adjusted RR 0.98; 95% CI 0.67–1.12; p = 0.04). In contrast, continuous combined HRT (with norethisterone, NETA) was associated with the highest risk of MI in this study (adjusted RR 1.35; 95% CI 1.18–1.53).

There is evidence that HRT may reduce the incidence of new-onset diabetes. Diabetes is a major risk factor for MI; indeed, individuals with diabetes are not only at increased risk of an MI, but have higher mortality after an MI33, as well as being at higher risk of recurrent cardiovascular events34. Approximately 30% of patients admitted to hospital with an acute MI have diabetes33. Analysis of the French cohort of women enrolled in E3N (n = 63 624) demonstrated a significant 18% reduction in the incidence of new-onset diabetes in women who had received HRT compared with never-users (adjusted HR 0.82; 95% CI 0.72–0.93)36. The incidence of new-onset diabetes was significantly reduced with both oral
and transdermal estrogens. When progestogens were also administered, a significant reduction in the risk of new-onset diabetes was seen in women receiving transdermal estradiol and micronized progesterone (HR adjusted for BMI during follow-up rather than baseline 0.67; 95% CI 0.54–0.84), oral estrogens combined with cyproterone acetate (HR 0.44; 95% CI 0.23–0.85) or with NETA (HR 0.44, 95% CI 0.26–0.75) only, compared with never-users.

**STROKE**

In the WHI study, unopposed oral estrogen (CEE) increased the risk of stroke by 39%, but the 95% CIs crossed 1 (HR 1.39; adjusted 95% CI 0.97–1.99)3. The addition of MPA to CEE also non-significantly increased the risk of stroke (HR 1.41; adjusted 95% CI 0.86–2.31)2.

The mechanisms of stroke associated with HRT

Stroke associated with HRT is one of the most difficult areas to study. In older women in whom atherosclerotic plaques have formed, the mechanism underlying both ischemic stroke and MI associated with HRT is thought to be related to atherosclerotic plaque instability and rupture leading to thrombosis37. Plaque pathophysiology is a complex area. Simplistically, the stability of an atherosclerotic plaque is provided by the extracellular matrix and a thick fibrous collagen cap38. Inflammation in a plaque, with the accumulation of macrophages, leads to the release of matrix metalloproteinases (MMPs) that digest collagen, thinning the fibrous cap and destabilizing the plaque38. Although stroke (and MI) associated with HRT in older women may be related to atherosclerotic plaque instability, this mechanism does not explain the increased risk of stroke in younger postmenopausal women receiving oral estrogen.

The ‘timing hypothesis’ states that oral estrogens have different effects on the biology of the vessel wall cells and inflammatory cells that accrue as atherosclerosis progresses, dependent upon the stage of the disease, i.e. early vs. late (Figure 2)39. In early atherosclerosis, oral estrogens have beneficial effects whereas, in established atherosclerosis, oral estrogens increase MMP levels, so destabilizing the plaque. This timing hypothesis supports the different mechanisms of stroke in younger and older women receiving HRT, which is further supported by data from a substudy of the WHI study that showed a reduced calcified plaque burden in younger women (aged 50–59 years) receiving estrogens compared with those receiving placebo (p = 0.02)40. Furthermore, it seems implausible that younger women have increased unstable cerebral atherosclerosis in the presence of estrogen, while estrogen exerts a protective effect against coronary atherosclerosis, particularly as atherosclerosis of the cerebral arteries is believed to occur much later in the sequence of atherosclerotic progression than coronary atherosclerosis37. It has been suggested that the mechanism underlying stroke associated with HRT in younger women is, at least in part, thrombotic rather than atherogenic in nature and, although estrogens may confer some protective effect on the cerebral vasculature, as they do in the coronary vasculature of younger women, the effect is probably overwhelmed by any thrombotic assault37.

Transdermal estradiol has been shown to reduce concentrations of monocyte chemoattractant protein-1 (MCP-1), which are related to the progression of atherosclerosis by enhancing MMP production, reducing the concentrations of other vascular markers of inflammation (cell adhesion molecules), and improving endothelial function in postmenopausal women41. Transdermal estradiol has no effect on C-reactive protein concentrations, which stimulate the expression of MCP-1 and cell adhesion molecules in endothelial cells41. In contrast, oral estrogens increase C-reactive protein concentrations, suggesting a possible direct effect on the synthesis of C-reactive protein in the liver during the first-pass metabolism of oral estrogen, which is avoided by transdermal administration.

**Transdermal estradiol and stroke risk: clinical data**

The limited clinical evidence available investigating the effects of transdermal estradiol on stroke risk indicates that the risk is not increased42. In a nested case–control study using the GPRD including 15 710 cases of stroke and almost 60 000 randomly selected, matched controls from women aged 50–79 years, transdermal estradiol was not associated with an increased risk of stroke, while oral estrogens significantly increased the risk (Table 1)42. When analyzed by dose, standard or low doses of transdermal estradiol (≤ 50 μg) did not increase the risk of stroke (adjusted rate ratio 0.81; 95% CI 0.62–1.05), but both low and high doses of oral estrogen did (adjusted rate ratio 1.25; 95% CI 1.12–1.40 and 1.48; 95% CI 1.16–1.90, respectively). There are experimental data suggesting that transdermal estradiol may exert its antiatherosclerotic effect by reducing the concentrations of inflammatory markers that contribute to plaque destabilization and improving endothelium-dependent vasodilation in the brachial arteries, which is expected to reflect the situation in the coronary arteries, in postmenopausal women41.

**Progestogens and stroke risk**

The choice of progestogen for those requiring combined HRT may also affect plaque physiology and endothelial function, with different effects associated with different progestogens43. In a study using human coronary cell cultures, MPA and NETA did not negatively influence the reduction in the concentration of adhesion molecules associated with estrogen, and NETA, but not MPA, reinforced the reduction in MCP-1 associated with estrogen43. Furthermore, both MPA and NETA enhanced the reduction in pro-MMP-1 (a precursor to MMP-1) associated with estrogen.
Hypertension is a major risk factor for CHD and stroke. Micronized progesterone appears to have a neutral or beneficial effect on blood pressure in postmenopausal women. In a small, randomized, double-blind, placebo-controlled, cross-over study, micronized progesterone alone did not affect blood pressure or any other measure of vascular function in healthy postmenopausal women. In the larger, randomized, double-blind, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) study, micronized progesterone combined with CEE did not affect blood pressure. In addition, in another small, short-term, double-blind, placebo-controlled study, micronized progesterone alone significantly reduced blood pressure in postmenopausal women with mild to moderate hypertension. Furthermore, in postmenopausal Korean women, micronized progesterone offset the daytime blood pressure increase (diastolic and systolic) associated with CEE in normotensive women, and potentiating the reduction in systolic blood pressure associated with CEE in hypertensive women. Moreover, in contrast to other progestogens, progesterone has been shown to antagonize the effect of aldosterone, causing natriuresis and a reduction in blood pressure (reviewed by Boschitsch and colleagues).

CONCLUSIONS

Unlike oral estrogens, transdermal estradiol does not increase the risk of VTE and, unlike some progestogens, the addition of micronized progesterone does not increase VTE risk. Transdermal estradiol appears to have a cardioprotective effect in postmenopausal women and significantly reduces the incidence of new-onset diabetes, a significant risk factor for MI, when used alone and in combination with micronized progesterone. Transdermal estrogen does not increase the risk of stroke, unlike oral estrogens. Furthermore, micronized progesterone has a neutral or beneficial effect on...
blood pressure; hypertension is a major risk factor for CHD and stroke. The implications of these changes on the current guidelines for the management of postmenopausal women are discussed elsewhere in this Supplement by Simon.

In conclusion, both experimental and clinical data indicate that transdermal estradiol in association with natural micronized progesterone could represent the optimal HRT, particularly in women at risk of cardiovascular adverse events.

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