**Effects of hormone therapy on blood pressure**

Zeinab Issa, MD, Ellen W. Seely, MD, Maya Rahme, MSc, and Ghada El-Hajj Fuleihan, MD, MPH

**Abstract**

**Objective:** Although hormone therapy remains the most efficacious option for the management of vasomotor symptoms of menopause, its effects on blood pressure remain unclear. This review scrutinizes evidence of the mechanisms of action of hormone therapy on signaling pathways affecting blood pressure and evidence from clinical studies.

**Methods:** Comprehensive Ovid MEDLINE searches were conducted for the terms “hypertension” and either of the following “hormone therapy and menopause” or “selective estrogen receptor modulator” from year 2000 to November 2013.

**Results:** In vitro and physiologic studies did not reveal a clear deleterious effect of hormone therapy on blood pressure. The effect of oral therapy was essentially neutral in large trials conducted in normotensive women with blood pressure as primary outcome. Results from all other trials had several limitations. Oral therapy had a neutral effect on blood pressure in hypertensive women. Transdermal estrogen and micronized progesterone had a beneficial effect on blood pressure in normotensive women and, at most, a neutral effect on hypertensive women. In general, tibolone and raloxifene had a neutral effect on blood pressure in both hypertensive and normotensive women.

**Conclusions:** Large randomized trials are needed to assess the effect of oral hormone therapy on blood pressure as a primary outcome in hypertensive women and the effect of transdermal preparations on both normotensive and hypertensive women. Transdermal preparations would be the preferred mode of therapy for hypertensive women, in view of their favorable physiologic and clinical profiles. The decision regarding the use of hormone therapy should be individualized, and blood pressure should be monitored during the course of treatment.

**Key Words:** Hormone treatment – Hypertension – Menopause – Blood pressure – Selective estrogen receptor modulators.
or which are expressed in vascular endothelial cells. The gene had higher systolic BP (SBP), with a mean...and evaluated individually.


either lower or raise BP, depending on the pathway involved. This section will mainly address the effects of estrogen and progesterone on BP from a pathophysiologic point of view and is followed by a clinical section that discusses the main relevant RCTs that focus on this topic.

PHYSIOLOGIC EFFECTS OF ESTROGEN ON THE VASCULAR SYSTEM

Estrogen can exert its effect on the heart and vessels through its two receptor isoforms, estrogen receptor (ER)-α and ER-β,4,5 which are expressed in vascular endothelial cells and vascular smooth muscle cells. The functional properties of ER-α and ER-β are different, and their effects can be mediated through genomic6 or nongenomic7 mechanisms (Fig.). The genomic mechanism occurs during a relatively long period and consists of binding of estrogen to ER elements on promoter regions of the target gene, thereby regulating the transcription of the target gene.9 The nongenomic mechanism has been the subject of multiple studies in recent decades. These so-called extranuclear actions are mediated through ERs located at or near the plasma membrane, which, once activated, interact with some membrane-associated signaling molecules such as ion channels, G-proteins, the tyrosine kinase c-Src, and the epidermal growth factor receptor, leading to the activation of a cascade involving mitogen-activated protein kinase, phosphatidylinositol 3-OH kinase, small GTPase RhoA, and protein kinase A/C, which might cause different actions like vasodilation but also may affect gene expression through the so-called “two-step model of sex steroid signaling.”10 ER-β-deficient male and female mice have been shown to develop hypertension and exaggerated vasoconstrictor response to β adrenergic receptor agonists.11

Certain polymorphisms in ER-β genes have been demonstrated to correlate with BP elevations in both women and men. In a study of 187 healthy postmenopausal women, those who had at least one allele with 26 cytosome-adenine repeats on the ER-β gene had higher systolic BP (SBP), with a mean difference of 10 mm Hg (P = 0.032), compared with those who did not.12 In the Framingham Heart Study, men with specific polymorphisms in the ER-α gene had higher SBP, and those with variations in ER-α nuclear receptor coactivator 1 and aromatase genes had a higher pulse pressure than those who did not have these specific polymorphisms. Women with polymorphisms in ER-α, aromatase, and nuclear receptor coactivator 1 genes also had higher diastolic BP (DBP).13

A newly discovered seven-transmembrane spanning intracellular G-protein–coupled ER (GPER), which is expressed throughout the cardiovascular system, may play an important role in BP modulation. The activation of this receptor was shown to reduce BP in ovariectomized mice14 and, conversely, GPER-deficient mice had increased endothelial prostanoid-mediated vasoconstriction.15 17β-Estradiol (E2) is a primary ligand for GPER; thus, decreasing E2 levels in menopause may be implicated in the pathophysiology of hypertension through this receptor.16

The effect of estrogen on target cells and organs, including the vascular system, is thus regulated by a complex interplay of genomic and nongenomic signaling mechanisms, and the integrated action of these machineries has important functional roles in a variety of pathophysiologic processes. Although there are various types of oral and transdermal estrogen preparations that can activate the genomic and nongenomic pathways detailed...
EFFECTS OF HORMONE THERAPY ON BLOOD PRESSURE

FIG. The multifaceted mechanisms of estrogen involve (1) acting on estrogen receptor (ER)-α and ER-β to reduce synthesis of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase and to increase synthesis of endothelial nitric oxide synthase (eNOS) and superoxide dismutase (SOD), thereby decreasing superoxide and increasing nitric oxide (NO) production and bioavailability (genomic effect); (2) rapidly activating eNOS via a calcium (Ca)-mediated mechanism without altering gene expression (nongenomic effect), leading to NO/cyclic guanosine monophosphate release and vascular relaxation; (3) activating protein kinase B (AKT) via MAP kinase (MAPK)–phosphorylatedinositol 3-OH (PI3) kinase pathways, reducing apoptosis and enhancing cell survival; and (4) reducing nuclear factor κB (NF-κB) activation/translocation via P38α-mediated p35 phosphorylation and c-Jun N-terminal kinase (JNK) 1/2–mediated signaling pathways, inhibiting chemokine/cytokine transcription and decreasing inflammation. In addition, estrogen acts on the membrane-bound and G-protein–coupled estrogen receptor GPR30 associated with transactivation of epidermal growth factor receptors (EGFR), which induces rapid signal transduction, including activation of MAPK, protein kinase A, and PI3 kinase, leading to cardiovascular protection. GSH3β, glutathione 3β. Reprinted from Yang and Reckelhoff

Mechanisms through which estrogen would lower BP

Estrogen and vascular tone

Menopause and its associated low estrogen state are characterized by endothelial dysfunction,

which can thus predispose to hypertension.

A study of 952 apparently healthy postmenopausal women (mean age, 53 y) followed for a mean of 3.6 years demonstrated that endothelial dysfunction, assessed by flow-mediated dilatation, preceded and predicted hypertension.

Aging per se is associated with a decline in endothelial function in normal humans, and this decline seems to occur earlier in men than in women. However, in women, a steep decline occurs at around the time of menopause, consistent with loss of a protective effect of estrogen on the arterial wall.

The postmenopausal state is indeed associated with a significant reduction in nitric oxide activity, and vasodilation is one of the most important effects of estrogen on arterial vessels. Estrogen-induced vasodilation has been described in animal models and clinical studies and occurs through activation of the endothelial nitric oxide synthase and release of nitric oxide through genomic and nongenomic signal transduction pathways.

Other possible mechanisms that have been implicated in the vasodilatory effect of estrogen are release of prostaglandin 2, stimulation of neuronal nitric oxide synthase in vascular smooth muscles cells, and inhibition of voltage-dependent L-type calcium current in vascular smooth cells.

Short-term sublingual administration of 17β-E2 1 mg was shown to improve vasodilatory responses in eight mildly hypertensive postmenopausal women (mean age, 54.4 y) who had no other risk factors for cardiovascular disease.

The effect of 17β-E2 2 mg/day, alone or combined with the progestin medroxyprogesterone acetate (MPA) 5 mg/day, on the function and morphology of isolated resistance arteries was assessed in a randomized placebo-controlled trial in 55 healthy postmenopausal women (mean age, 57 y) before and after 3-month therapy with 17β-E3, MPA acetate, and 17β-E2 plus MPA acetate or placebo. E2 increased artery flow–mediated dilatation, improved endothelial cell morphology, increased the expression and phosphorylation of the actin binding protein myosin and of the focal adhesion complex controller, induced the rearrangement of cytoskeletal actin and vinculin fibers, promoted endothelial cell horizontal migration, and decreased signs of endothelial apoptosis. Some of these beneficial effects were preserved with the addition of MPA, whereas MPA alone failed to augment artery flow–mediated dilatation and to improve endothelial cell morphology and apoptosis.

Healthy postmenopausal women receiving oral 17β-E2 2 mg/day combined with micronized progesterone 200 mg/day had improved carotid artery compliance.

Similarly, in a 12-month RCT, transdermal E2, but not oral CEE therapy, had a beneficial effect on arterial stiffness but had no effect on BP.

However, the beneficial effect of estrogen on flow-mediated vasodilation has not been consistent across studies.

The discrepancy in the results may be related to differences in age, timing of initiation of estrogen after menopause, and preparations of estrogen and progestins.
Estrogen and the kinin-kallikrein system

Increase in the activity of the kinin-kallikrein system leads to lowering of BP, and HT may affect this system. HT in the form of oral 17β-E2 (2 mg), alone or combined with continuous MPA, increased urinary kallikrein excretion in 39 normotensive postmenopausal women after 3 months of E2 (P < 0.001) and E2 with MPA (P < 0.01), whereas it decreased nonsignificantly in the placebo group (P > 0.06). Although there were no significant BP changes after 3 months of therapy, there was a significant negative correlation between urinary kallikrein and mean arterial pressure and pulse pressure in the estrogen-alone arm.31

Estrogen and ANP

E2 was shown to increase ANP, a molecule with a wide array of cardiovascular and renal effects, including natriuresis, diuresis, and antagonism of the renin-angiotensin system and the sympathetic nervous system, which could lower BP.32 E2 also decreased ANP clearance and reduced weight gain in folliculotropin receptor knockout mice, an animal model for obesity and hypertension.33 The increase in ANP induced by E2 was accompanied by a reduction in BP in ovariectomized spontaneously hypertensive rats.34

Estrogen and inflammation

Indirect evidence suggests that inflammation may modulate BP in animal models. Angiotensin II–induced hypertension was attenuated in interleukin-6 knockout mice.35 Similarly, in pregnant rats with elevated tumor necrosis factor-α levels, etanercept, a tumor necrosis factor-α–soluble receptor inhibitor, significantly reduced BP.36 Estrogen has been shown to have a suppressive effect on E-selectin, cell adhesion molecules, monocyte chemoattractant protein-1, and tumor necrosis factor-α; inconsistent effects on interleukin-6; and stimulatory effects on vasoprotective cytokines such as transforming growth factor-α,37 in addition to attenuating vascular expression of inflammation-associated genes.38 Thus, estrogen may have BP-lowering effects through these mechanisms.

Mechanisms through which estrogen would increase BP

Estrogen and the RAAS

The RAAS has powerful effects on BP through multiple mechanisms mediated by angiotensin II. These include the promotion of sodium and water reabsorption via stimulation of aldosterone release, systemic arteriolar vasoconstriction, promotion of endothelial dysfunction, stimulation of the sympathetic nervous system, and decrease in vagal tone. In addition, angiotensin II has direct powerful inotropic, chronotropic, and hypertrophic effects on the heart. Estrogen can regulate several of the components of the RAAS.

Oral estrogens induce an increase in the hepatic production of angiotensinogen (renin substrate).39 However, not all the effects of estrogen are stimulatory after this step. The rise in angiotensinogen is typically associated with a compensatory fall in renin and maintenance of angiotensin I levels modulated by a negative feedback loop system.

Angiotensin I is converted into angiotensin II (the active peptide) by angiotensin-converting enzyme (ACE), which is present in the lung and other tissues. Oral estrogen has been demonstrated to lower ACE levels. However, in several studies, despite lower ACE levels, levels of angiotensin II were higher in the presence of estrogen,40,41 thus suggesting that conversion into angiotensin II may occur via non-ACE pathways. This increase in angiotensin II would be expected to increase BP. However, whether oral estrogen increases BP may depend on the relative activation of the different components of the RAAS and on the intactness of compensatory mechanisms to compensate for an increase in angiotensin II. In a study by Seely et al,41 21 normotensive and 10 hypertensive women received either oral CEE (0.635 mg) or droloxifene (60 mg/d), a SERM, for a period of 16 weeks. Oral CEE increased angiotensinogen levels, decreased active renin and ACE levels, and kept angiotensin I levels unchanged. Both CEE and droloxifene significantly increased plasma-immunoreactive angiotensin II levels without a change in BP. Other studies supported a fall in circulating ACE levels with oral estrogen.42

Although oral estrogen increases angiotensinogen levels, transdermal estrogen does not. Transdermal E2 at a dose of 0.2 mg twice a week had no significant effect on plasma renin activity or aldosterone levels in healthy postmenopausal women.43 This neutral effect of transdermal E2 on the RAAS was shown in multiple studies.44–46

Angiotensin mediates its effects by binding to the angiotensin type I receptor (AT1R). The effects of estrogen on AT1R are conflicting. Estrogen can induce a decrease in AT1R expression in kidneys and vessels associated with a fall in BP, with restoration of estrogen, in an ovariectomized animal model.47 In contrast, in an animal model that was pretreated with an inhibitor of nitric oxide, o-nitro-L-arginine-methyl-ester, to create a model of vascular “aging,” administration of E2 to ovariectomized animals increased AT1R protein in the kidney, and this increase was positively associated with an increase in proteinuria.48 Therefore, the effect of estrogen on AT1R may depend on the state of the underlying vasculature. Furthermore, oral estrogen has also been suggested to antagonize angiotensin II receptor–mediated growth-promoting effects on vascular smooth muscle cells.49

Estrogen’s effect on the RAAS is thus complex and involves both stimulatory and inhibitory actions. Estrogen’s effect on the RAAS results in changes in BP that may depend on the relative balance between these actions, the health of the underlying vasculature, and the ability of other homeostatic systems to compensate for ensuing changes in RAAS activity.

Given estrogen’s complex relationship with the RAAS, it is no surprise that estrogen administration has been demonstrated to influence antihypertensive response to agents that interrupt the RAAS. Garcia et al50 showed that in spontaneously hypertensive rats, the antihypertensive effect of the converting enzyme inhibitor captopril was enhanced when oral E2 was added; the combination—not captopril alone—inhibited
extracellular signal–regulated kinase 1/2 phosphorylation, which mediates angiotensin II–induced arterial muscle proliferation. The AT1R blocker candesartan given to normotensive postmenopausal women resulted in a further decrease in BP in the group receiving oral HT (CEE and MPA) versus those not receiving any.\(^{51}\) Furthermore, the AT1R blocker irbesartan added to oral E\(_2\) caused a 5–8 mm Hg decrease in both SBP and DBP in a higher percentage of hypertensive postmenopausal women compared with irbesartan alone and in addition to a significant decrease in aldosterone levels.\(^{52}\)

### Estrogen and the sympathetic system

Activation of the sympathetic system can lead to hypertension by causing vasoconstriction and by increasing renal tubular sodium reabsorption.\(^{53}\) Postmenopausal status is associated with increased sympathetic activity through several mechanisms. First, obesity, which is common in postmenopausal women, can increase sympathetic activity, which, in the kidney, leads to increased renin release and vasoconstriction that can contribute to hypertension.\(^{54}\) Increased leptin levels found in obese women also activate the sympathetic system via activation of melanocortin receptors in the hypothalamus,\(^{55,56}\) and obese postmenopausal women have a greater predilection for hypertension than lean postmenopausal women.\(^{57}\) Furthermore, anxiety and depression, which are more common in women than in men, can activate the sympathetic system and elevate BP mainly in individuals with metabolic syndrome and hypertension. Oral estrogen therapy may decrease sympathetic nerve activity.\(^{30}\)

In summary, postmenopausal women are at increased risk for sympathetic overactivity induced by obesity, increased leptin levels, and anxiety, an effect that may be counteracted by estrogen therapy.

### POTENTIAL ROLE OF PROGESTINS IN BP REGULATION

We evaluated studies investigating the effects of progestins on the vascular system and found conflicting results,\(^{60}\) possibly owing to differences in the type of progestin used, the route of administration (oral vs transdermal), and the vascular markers determined, the clinical relevance of which is still controversial. Indeed, different classes of progestins differ in their metabolic, androgenic, glucocorticoid, and antimineralocorticoid effects, as detailed in Table. The class properties for each of the progestins detailed in Table (eg, androgenic, glucocorticoid, and mineralocorticoid) were derived from different studies that used differing methodologies and are thus mostly qualitative and not directly comparable between the compounds listed.

Szmuiłowicz et al\(^{52}\) studied pressor and renovascular responses to infused angiotensin II, a potent vasoconstrictor, in 34 hypertensive postmenopausal women not on HT and off all antihypertensive therapies for at least 2 weeks. The vasoconstrictor response to angiotensin II was blunted in women with higher endogenous progesterone levels on low sodium balance, an effect that was independent of age, body mass index, and E\(_2\) concentration. Therefore, the presence of endogenous progesterone in premenopausal women, with levels ranging

<table>
<thead>
<tr>
<th>Progesterone Progestogenic Antigonadotropic Antiestrogenic Estrogenic Androgenic Antiandrogenic Glucocorticoid Antimineralocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestosterone</td>
</tr>
<tr>
<td>Dydrogesterone</td>
</tr>
<tr>
<td>Medrogestone</td>
</tr>
<tr>
<td>17α-Hydroxyderivatives</td>
</tr>
<tr>
<td>Chlormadinoneacetate</td>
</tr>
<tr>
<td>Cyproteroneacetate</td>
</tr>
<tr>
<td>Megestrolacetate</td>
</tr>
<tr>
<td>Medroxyprogesteroneacetate</td>
</tr>
<tr>
<td>19-Norprogesterone derivates</td>
</tr>
<tr>
<td>Nomegestrolacetate</td>
</tr>
<tr>
<td>Promegestone</td>
</tr>
<tr>
<td>Trimegestone</td>
</tr>
<tr>
<td>Spirolactone derivates</td>
</tr>
<tr>
<td>Drosperinone</td>
</tr>
<tr>
<td>19-Nortestosterone derivates</td>
</tr>
<tr>
<td>Norethisterone</td>
</tr>
<tr>
<td>Lynestrenol</td>
</tr>
<tr>
<td>Norethinodrel</td>
</tr>
<tr>
<td>Levonorgestrel</td>
</tr>
<tr>
<td>Norgestimate</td>
</tr>
<tr>
<td>3-keto-Desogestrel</td>
</tr>
<tr>
<td>Gestodene</td>
</tr>
<tr>
<td>Dienogest</td>
</tr>
</tbody>
</table>

(*) Effective; (±) weakly effective; (–) not effective.

Reprinted from Schindler et al\(^{61}\) with permission of the publisher. Copyright © 2008, Elsevier.
between 10 and 20 ng/dL, may blunt a predisposition to hypertension, a protective effect that may be lost in menopause.\(^{62}\)

MPA is the most commonly used progestin in studies evaluating the impact of HT on cardiovascular outcomes. It is 17α-hydroxyprogesterone derivative, which is weakly effective as an antiandrogenic agent with no antimineralocorticoid activity.\(^{61}\) The administration of MPA with estrogen has been shown to attenuate estrogen’s augmentation of endothelium-dependent vasodilation.\(^{63}\) In the PEPI trial,\(^{64}\) 875 healthy postmenopausal women aged 45 to 64 years were randomly assigned to five groups: placebo; CEE 0.625 mg/day; CEE 0.625 mg/day plus cyclic MPA 10 mg/day for 12 days/month; CEE 0.625 mg/day plus consecutive MPA 2.5 mg/day; or CEE 0.625 mg/day plus cyclic micronized progesterone 200 mg/day for 12 days/month. SBP, which was among the primary outcomes, did not vary between the MPA arm and the micronized progesterone arm.

The addition of the oral progestin norethisterone to estrogen has been shown to antagonize the vasodilatory effects of estrogen in postmenopausal women, as measured by the prostacyclin/thromboxane quotient,\(^{65}\) a factor that is known to be crucial for the relationship of vasorelaxation to vasoconstriction.

A new spironolactone derivative progestrone, drospirenone (DRSP), was found to have antimineralocorticoid and anti-androgenic activities.\(^{61}\) The addition of DRSP 3 mg to oral 17β-E\(_2\) 1 mg in women with stage 1 hypertension resulted in a mean reduction in clinic BP to \(-14.1/7.9\) mm Hg with DRSP/E\(_2\) and \(-7.1/4.3\) mm Hg with placebo (\(P < 0.000\) for both SBP and DBP). A similar pattern was noted on 24-hour ambulatory BP (AmBP) monitoring in a subset of women with decrements of \(-8.5/4.2\) mm Hg with DRSP/E\(_2\) versus \(-1.8/1.6\) mm Hg with placebo (\(P = 0.002\) for SBP and \(P = 0.07\) for DBP vs placebo).\(^{66}\) BP measurements reached their lower limits within 2 months of therapy, and there was no significant difference in potassium levels from baseline or in the incidence of hyperkalemia in the DRSP/E\(_2\) group compared with placebo. These results were confirmed in another RCT\(^{67}\) that tested three doses of DRSP combined with oral E\(_2\), oral E\(_2\) alone, and placebo in 750 postmenopausal women with stage 1 to stage 2 hypertension (mean [SD] age, 57 [6] y). Mean (SD) systolic AmBP (\(-6.1\) [11.2], \(P < 0.0001\)) and diastolic AmBP (\(-3.5\) [7.1], \(P < 0.0001\)) decreased significantly versus placebo mainly in the DRSP 3 mg/E\(_2\) group. Nevertheless, thromboembolic events remain a concern with the use of DRSP, as shown in a recent analysis from the Danish cohort study, where the rate ratio (95% CI) of confirmed venous thromboembolism for users of oral contraceptive pills containing DRSP was 2.1 (1.6-2.8) compared with levonorgestrel as reference.\(^{68}\) Whether these findings are applicable to the lower doses of DRSP/E\(_2\) in HT regimens is not known.

Dydrogesterone is a retroprogesterone, which seems to be a highly selective progestin with neutral activity in glucocorticoid, androgen, and aldosterone receptors.\(^{61}\) The addition of dydrogesterone to E\(_2\) did not affect the serum levels of endothelin (a potent vasoconstrictor) compared with E\(_2\) alone in postmenopausal women with more than two risk factors for coronary artery disease.\(^{69}\) Furthermore, in contrast to MPA, dydrogesterone was shown to have a neutral effect on E\(_2\)-induced positive effect on nitric oxide synthase activity and expression in human endothelial cells from the umbilical vein and has favorable effects on inflammatory markers in postmenopausal women. Dydrogesterone (at a dose of 10 mg for 14 d of each 28-d cycle) given sequentially with E\(_2\) 1 mg was shown to decrease ambulatory SBP by 5 mm Hg after 12 months of treatment, compared with no treatment, in healthy postmenopausal women.\(^{70}\) Similarly, dydrogesterone 10 mg/day given sequentially with oral E\(_2\) 1 mg caused significant falls in SBP and DBP in 35 mildly to moderately hypertensive postmenopausal women versus no treatment.\(^{75}\) These findings need to be confirmed in larger randomized studies.

Furthermore, Honisett et al\(^{76}\) evaluated the effects of micronized progesterone (100 mg daily) for 6 weeks on vascular function and BP in a randomized placebo-controlled trial of 20 healthy postmenopausal women. Micronized progesterone did not affect vascular function (as assessed by flow-mediated dilation of the brachial artery, systemic arterial compliance, and cutaneous vascular reactivity), nor did it change BP.

In summary, as progestins differ in their BP effects, studies of the effects of combined HT on BP may be affected by the progestin used. Endogenous progesterone, micronized progesterone, dydrogesterone, and DRSP may have BP-lowering effects through both direct vascular actions and diuretic properties.\(^{77}\)

**MENOPAUSAL TRANSITION, HT, AND BP**

Menopausal transition has been associated with changes in BP, and several studies evaluating the impact of HT on BP in postmenopausal women are described herein.

The change in BP across menopause was evaluated in a large cross-sectional study (Study on Hypertension Prevalence in Menopause in the Italian Population) of 18,326 Italian women aged 46 to 59 years. SBP and DBP were significantly higher (3.4 and 3.1 mm Hg, respectively) in postmenopausal women than in perimenopausal and premenopausal women at the younger end of the age range even after adjustment for age, body mass index, and other confounding factors.\(^{78}\)

The Multi-Ethnic Study of Atherosclerosis included 610 normotensive American postmenopausal women who were followed to assess change in BP and development of incident hypertension during a mean follow-up of 4.8 years (maximum, 6.7 y). One hundred ninety-four women developed incident hypertension. Higher endogenous E\(_2\), testosterone, and dehydroepiandrosterone levels and lower sex hormone-binding globulin levels were associated with a higher incidence of hypertension and greater longitudinal rise in BP after adjusting for age, race/ethnicity, and lifestyle factors. Adjustment for body mass index eliminated the associations for E\(_2\) and testosterone but only attenuated the associations for dehydroepiandrosterone and sex hormone–binding globulin. The associations for E\(_2\), testosterone, and dehydroepiandrosterone were therefore mostly explained by adiposity, whereas the association for sex hormone–binding globulin was independent.
EFFECTS OF HORMONE THERAPY ON BLOOD PRESSURE

of measures of adiposity, insulin resistance, and systemic inflammation.79

Much of the concern with the impact of HT on BP originates from data that relate oral contraceptives to hypertension in younger women, although the specific hormonal compounds (be it estrogens and progestins) used for HT replacement differ and may not have the same effects on BP. Specifically, ethinyl E2 is commonly used in oral contraceptives and has a very potent effect on hepatic production of angiotensinogen.80

In the literature, there is significant variability in the effect of HT on BP. This inconsistency among studies could be attributable to the different designs, sample sizes, types of HT, and methods used to measure BP; type of menopause (surgical vs natural); and participant characteristics, including phase in the menopausal transition and endogenous hormonal profile.

HT in normotensive women

Studies evaluating the effect of HT on BP in normotensive postmenopausal women varied in design between case-control studies, prospective studies, and RCTs.

In our literature review of case-control and prospective studies, there was variability in the estrogen-progesterone preparations used and in the means of BP measuring (ambulatory vs clinic BP). A neutral or lowering effect of HT on BP was the main outcome of these studies.31-66 Likewise, a review by Mueck and Seeger,87 which summarized comparative studies with 24-hour AmBP measurements in normotensive postmenopausal women from 1997 to 2002, revealed mainly a significant BP-lowering effect of HT. However, this review included studies that were not all randomized with different HT preparations, with predominant use of transdermal E2, which may be more beneficial than oral HT in relation to BP effects.77

Randomized trials

In the PEPI trial,64 875 healthy postmenopausal women were randomly assigned to CEE (0.625 mg) alone or in combination with progestin/CEE 0.625 mg (cyclic or continuous MPA, or cyclic micronized progesterone) versus placebo for 3 years. No significant difference in office SBP, a primary outcome, was seen between treatment groups and placebo. The Women’s Health Initiative (WHI) consisted of two parallel clinical trials and an observational study designed to test the effects of postmenopausal HT, diet modification, and calcium and vitamin D supplements on heart disease, fractures, breast cancer, and colorectal cancer. In one trial, women received oral CEE 0.625 mg with MPA 2.5 mg versus placebo, whereas in the other trial, they received CEE alone 0.625 mg versus placebo. The method for measuring BP was not specified. In the HT combination arm, SBP was 1.5 mm Hg higher at 2 years (P value not available), whereas DBP remained unchanged.88

In the estrogen-only arm, SBP increased by 1.1 mm Hg (P = 0.003) at 1 year compared with placebo, whereas DBP did not change.89 The increased risk of cardiovascular and cerebrovascular events observed in this trial had a major impact on HT use by postmenopausal women, but whether this was directly related to an increase in BP is still unknown because this variable was not measured as a primary outcome in the trial. HT (oral E2 2 mg with or without norethisterone 1 mg, according to hysterectomy status) had no effect on office SBP and DBP, which were measured as primary outcomes in the Danish Osteoporosis Prevention Trial, an open-label trial evaluating 1,006 postmenopausal women.90 Similarly, there was no difference in office BP between the HT group (unopposed oral 17β-E2 1 mg) and the placebo group at 2 years in the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), which evaluated 222 healthy postmenopausal women with the primary endpoint being BP and with the overall rate of progression of subclinical atherosclerosis measured by carotid artery intima-media thickness.91 Other smaller randomized controlled studies using AmBP measurement as primary outcome revealed similar neutral effects of oral HT on BP.41,92

For studies that specified BP as primary outcome in normotensive women on oral HT, the risk of bias was mostly concentrated between low risk and unclear risk (see Appendix II-B.1, Supplemental Digital Content 3, http://links.lww.com/MENO/A109). It was low for most bias criteria in EPAT and the PEPI trial,84,92 unclear in one study,41 and ranged from low to high in the studies by Vestergaard et al84 and Sorensen et al92.

Transdermal E2 may represent an attractive and safer option for postmenopausal women given its bypass of first hepatic pass, which is associated with increased triglycerides, C-reactive protein, and activation of coagulation.93 Seely et al13 evaluated the effect of transdermal E2 (two 0.1-mg patches twice a week), with or without progesterone (intravaginal micronized progesterone 300 mg/d added for 2 weeks), on BP in 15 healthy postmenopausal women. The duration of use was 8 weeks for transdermal E2 and 10 weeks for E2 and progesterone. Nocturnal SBP, DBP, and mean BP decreased significantly (P < 0.02) versus placebo. The high doses used in this study aimed at achieving levels similar to those seen in premenopausal women. The E2 levels achieved were similar to those of the early to middle follicular phases, and progesterone levels were compatible with those seen in the luteal phase. The addition of progesterone did not lead to any further change in day or night BP beyond that seen with E2 alone. Similarly, 12 postmenopausal women were randomly assigned to CEE 0.625 mg, transdermal E2 (two 0.1-mg patches twice a week, 200 μg/d), or placebo in a single-blind cross-over design. Although oral CEE did not result in a change in BP, transdermal E2 resulted in a decrease in DBP compared with placebo.94 This lowering of DBP was also evident in another randomized study by Ichikawa et al75 in 22 postmenopausal women.

The three transdermal E2 studies specified BP as a primary outcome, but they had a small number of participants (N = 24-30) and a wide range of risk-of-bias assessment (see Appendix II-B.1, Supplemental Digital Content 3, http://links.lww.com/MENO/A109). It ranged from low risk to unclear risk in two studies43,94 and from low risk to high risk in the third study.45

In summary, RCTs evaluating the effect of various oral HT preparations on BP as a primary outcome, such as PEPI trial (CEE/MPA/micronized progesterone), Danish Osteoporosis
Prevention Trial (17β-E2/norethisterone), EPAT (17β-E2), and smaller trials by Seely et al43 (CEE/micronized progesterone) and Sorensen et al42 (17β-E2/norethisterone), consistently revealed a neutral effect. Conversely, the WHI showed an increase in BP in the CEE/MPA and CEE-only arms; however, BP was not specified as a primary outcome. An essentially beneficial effect of transdermal E2 preparations on BP was noted in smaller trials,43,45,96 where BP was a specified primary outcome, but the risk of bias was suboptimal.

**HT in hypertensive women**

HT use in women with hypertension represents another challenge in relation to controversial data and the lack of randomized studies with BP as the primary endpoint. Instead, data are available from cross-sectional studies. One of the largest cross-sectional studies, the Rancho Bernardo Study, consisted of two components—a cross-sectional study of 1,044 participants and a 10-year prospective follow-up of 443 women—that evaluated the association between postmenopausal oral estrogen therapy and BP, renal function, and proteinuria.95 In the cross-sectional study, DBP was highest in never users (age-adjusted P = 0.07; multivariate-adjusted P = 0.01), but SBP did not differ by postmenopausal estrogen status after adjustment for covariates (age, weight, smoking, and hypercholesterolemia). On prospective analysis, SBP did not differ in the past and current estrogen user groups, but never users exhibited an age-adjusted increase in SBP across time (mean increase, 6 mm Hg; P = 0.02), and the difference persisted after multivariate adjustment. DBP of never users showed no significant age-adjusted change (P = 0.1), whereas past users (age-adjusted P < 0.0001) and current users (age-adjusted P < 0.0001) showed similar declines in their DBP. Other observational studies showed either a neutral or a beneficial effect of HT on BP.

**Randomized trials**

In a randomized trial by Kaya et al75 evaluating 66 postmenopausal women, AmBP, a primary outcome, fell significantly in the group of women treated with HT (micronized 17β-E2; 1 mg/d sequentially combined with dydrogesterone 10 mg/d for 14 d of each 28-d cycle). Other randomized trials showed mainly no effect of varying HT regimens on BP, which was a primary outcome in all of these studies.29,91,99,100 The effect of HT (CEE and MPA) on the secondary prevention of coronary heart disease (CHD) was evaluated in HERS, a randomized placebo-controlled trial where 39% of women were hypertensive.101 For 4.2 years, office SBP increased by 1 mm Hg (P < 0.0001), whereas office DBP remained unchanged in HT-treated women (CEE 0.625 mg and MPA 2.5 mg) compared with placebo. Similarly, mean pulse pressure increased by 2 mm Hg (P = 0.04) in treated women versus placebo; however, BP and pulse pressure were not primary or secondary outcomes.102 In contrast, office DBP decreased significantly in the HT groups compared with the control group in the Postmenopausal Hormone Replacement Against Atherosclerosis (PHOREA) trial, which was designed to determine the effect of HT (oral 17β-E2 1 mg with standard-dose cyclic gestodene [oral gestodene 0.025 mg on days 17-28 of each 4-wk cycle] or oral 17β-E2 1 mg with low-dose gestodene [0.025-mg addition in each third cycle only]) or no treatment on the progression of atherosclerosis. Again, BP was not a primary outcome.103

It has been suggested that some women may paradoxically manifest an increase in BP in response to oral estrogen therapy. However, the only study to support such observation is HERS, and this may be explained by the fact that 40% of women were hypertensive at study entry. However, BP was not measured as primary endpoint in HERS.

For studies that specified BP as primary outcome in hypertensive women on oral HT, the risk-of-bias assessment spanned all ranges (see Appendix II-B.1, Supplemental Digital Content 3, http://links.lww.com/MENO/A109). It was low for most bias criteria in EPAT,91 mixed in three studies (unclear risk to low risk90 and low risk to high risk29,75), and mainly unclear in one study.100 The risk of bias in the other four large trials that did not have BP as primary outcome was low in HERS101 and spanned from low to high in the WHI 2002, WHI 2004, and PHOREA trial.88,89,103

The effect of transdermal estrogen on BP as a primary outcome has also been investigated in hypertensive women; unfortunately, the studies were small (N = 24-3029,104). They showed a neutral effect or a decrease in BP and differed in their pattern of decrease (systolic vs diastolic, daytime vs nighttime).29,104 The risk of bias was low to unclear in one study29 and low to high in the other104 (see Appendix II-B.1, Supplemental Digital Content 3, http://links.lww.com/MENO/A109).

In summary, four29,91,99,100 of five small RCTs evaluating the impact of oral HT on BP as a primary outcome in hypertensive women revealed a neutral effect on BP, and one study75 that used AmBP revealed a beneficial effect. Conversely, two large RCTs—HERS (CEE/MPA) and PHOREA trial (17β-E2/gestodene)—that did not have BP as a specified primary outcome revealed opposing results. Similar to findings in normotensive women, a beneficial effect of transdermal E2 preparations on BP was noted in two small trials in hypertensive women, where BP was a specified primary outcome, but their associated risk of bias was suboptimal.29,104 Thus the need for large randomized trials assessing the impact of transdermal and oral estrogen on BP in hypertensive women.

**SERMS, TIBOLONE, AND BP**

SERMs, or tissue-specific estrogens, act either as agonists or as antagonists on the ER, depending on the target tissue where they act. This family of synthetic compounds is designed to preserve the beneficial effects of estrogens on menopausal symptoms and bone, incur protection against cardiovascular diseases, and exert no undesired effects on reproductive organs. However, the search for the ideal SERM is still ongoing, as such compound remains elusive.105-108

**Raloxifene**

Raloxifene is a second-generation SERM and the only one approved by the Food and Drug Administration for prevention...
and treatment of postmenopausal osteoporosis and for reduction of the risk of invasive breast cancer in high-risk women.

Raloxifene was shown to reduce the risk of vertebral fractures, was associated with increased risks of venous thromboembolism and fatal stroke (but not stroke), and did not display any other adverse effect on cardiovascular diseases.\textsuperscript{109,110}

In a study by Morgante et al,\textsuperscript{111} raloxifene 60 mg/day did not affect the renin-angiotensin system or BP in 20 normotensive postmenopausal women and 20 hypertensive postmenopausal women (controlled with antihypertensive medications for 6 mo; mean age, 57 y). Sumino et al\textsuperscript{112} investigated the effects of raloxifene on components of the RAAS in 23 hypertensive and 18 normotensive postmenopausal women (mean [SD] age, 64.7 [7.3] y) with osteoporosis or osteopenia, who were divided into four groups. Eleven hypertensive and eight normotensive women received raloxifene (60 mg/d) for 6 months, and 12 hypertensive and 10 normotensive women did not receive raloxifene for 6 months. BP and all parameters of interest remained unchanged. Finally, administration of raloxifene 60 mg/day did not affect the 24-hour AmbP measurement in a 4-month placebo-controlled trial of 32 healthy postmenopausal women with osteopenia.\textsuperscript{113}

The Multiple Outcomes of Raloxifene Evaluation trial\textsuperscript{109} was designed to determine the effect of raloxifene on bone mineral density and vertebral fractures. Hypertension, captured as an adverse event, occurred in 9% in the placebo group compared with 6.9% in the raloxifene 60 mg group (\textit{P} = 0.01).

The Raloxifene Use for The Heart (RUTH) trial\textsuperscript{110} studied 10,101 postmenopausal women randomized to raloxifene 60 mg versus placebo for 5.6 years, and 78% of the participants were hypertensive. Approximately half of the women had CHD at baseline; the other half were enrolled based on CHD risk score, but BP was not a specified primary outcome. The primary objective of the RUTH trial was to determine the effects of raloxifene versus placebo on the incidence of coronary events and invasive breast cancer. No significant differences in SBP or DBP were observed between treatment groups,\textsuperscript{114} but raloxifene use was associated with increased risks of fatal stroke and venous thromboembolism. The incidence of fatal stroke did not differ among subgroups, except for an observed higher incidence of stroke associated with raloxifene use among current smokers. The increase in the incidence of fatal stroke in the RUTH trial remains a major concern in high-risk patients, and the lack of data relating therapy to BP further increases this concern.

\textbf{Bazedoxifene}

Bazedoxifene is a novel third-generation SERM that received European Medicines Agency approval for treatment of postmenopausal osteoporosis in women at high risk for fractures. BP was neither a measured endpoint nor a reported adverse event in the studies evaluating bazedoxifene.\textsuperscript{115,116}

\textbf{Lasoxifene}

Lasoxifene is a third-generation SERM that received European Medicines Agency approval for treatment of postmenopausal osteoporosis in women at high risk for fractures. The Postmenopausal Evaluation and Risk Reduction with Lasoxifene trial was a 5-year RCT comparing the effects of lasoxifene 0.25 or 0.5 mg with those of placebo in postmenopausal women with osteoporosis. BP changes were not reported.\textsuperscript{117}

\textbf{Tibolone}

Tibolone, a selective tissue estrogenic activity regulator, has been widely used in Europe as a substitute for HT during the menopausal transition because of its efficacy in relieving menopausal symptoms and its beneficial effect on bone mineral density, compared with placebo.\textsuperscript{106} But the increased risk of stroke associated with its use remains a major concern preventing its approval in many countries.

In small studies of normotensive postmenopausal women where BP was a primary outcome, tibolone had a neutral\textsuperscript{118,119} or lowering\textsuperscript{120} effect on BP. The significant improvement in BP among younger postmenopausal women in the study by Vassalle et al who received tibolone may be explained by the fact that they had menopausal symptoms, the relief of which may result in a concomitant decrease in BP.\textsuperscript{120} Lloyd et al\textsuperscript{121} studied the effect of tibolone 2.5 mg on BP in 29 hypertensive postmenopausal women for 6 months using a 2:1 randomization protocol design. The mean (SD) SBP declined by 5.30% (2.87%) versus 4.94% (3.37%), whereas DBP declined by 5.38% (2.65%) versus 0.85% (3.69%) with tibolone and placebo, respectively, but not significantly.

In the Long-Term Intervention on Fractures with Tibolone trial on 4,538 postmenopausal women, BP measurements were not detailed.\textsuperscript{122} In the Osteoporosis Prevention and Arterial effects of tiboLone study\textsuperscript{123} that included 866 healthy postmenopausal women, BP, which was not a specified outcome, was unchanged and did not differ between the three groups. It decreased by \(-0.5%\) in the tibolone (2.5 mg) group and by \(-0.7%\) in the CEE 0.625 mg/MPA2.5 mg group (placebo, \(P = \) not significant). Therefore, none of the trials—which were mostly conducted in older postmenopausal women, including one trial conducted in hypertensive women—revealed any increments in BP with tibolone. Limitations of these studies include their relatively short duration, small sample size (with the exception of the Long-Term Intervention on Fractures with Tibolone trial and the Osteoporosis Prevention and Arterial effects of tiboLone study, which did not measure BP as a primary outcome), and, thus, their low power to detect subtle BP changes, if any.

The risk-of-bias assessment for the 12 randomized trials that used SERMs ranged between low risk and unclear risk for most trials. Only five studies specified BP as a primary outcome (two with raloxifene\textsuperscript{112,113} and three with tibolone\textsuperscript{118,119,121}), with mixed results on risk-of-bias criteria for both raloxifene and tibolone (see Appendix II-B.2, Supplemental Digital Content 3, http://links.lww.com/MENO/A109).

In summary, data on the effect of SERMs and tibolone on BP are rather limited and restricted to raloxifene and tibolone. The effect was essentially neutral, regardless of trial size, whether BP was a specified primary outcome, and whether
studies evaluated normotensive or hypertensive women. The increased risk of fatal stroke in the RUTH trial, although a concern, was not documented to be related to BP.

OTHER HORMONAL PREPARATIONS

Other hormonal preparations, such as transdermal testosterone and phytoestrogens, have been studied to some extent in postmenopausal women, but their discussion is beyond the scope of this review. The Food and Drug Administration has not approved any androgen formulation for hypoactive sexual desire disorder pending long-term safety data (http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4082B1_02_B-FDA-Intrinsa-Medical-Review.pdf). The regulatory agencies in Europe have approved a testosterone patch (Intrinsa 300 µg) for women who had had surgical menopause, but it is no longer being manufactured as per Lexi-Comp (accessed May 2014).

CONCLUSIONS

Hypertension is a major risk factor for cardiovascular disease, and menopause by itself seems to be a risk factor for an increase in BP. The effect of estrogen, with or without progesterone, has been studied in postmenopausal women through observational and randomized trials. These studies varied in design, population, sample size, duration, and formulations used, and on whether BP was a specified primary outcome. The data for oral preparations were most robust in normotensive women (where BP was specified as a primary outcome and sample size was large) but had major limitations in all other subgroups.

In normotensive women, the effect of oral estrogen therapy on BP was neutral. These findings can be accepted with confidence in view of the fact that they were consistent across studies that had specified BP as a primary outcome, including two major large trials that had a low risk of bias (namely, PEPI trial and EPAT). The effect of transdermal therapy on BP was beneficial in normotensive women, whereas the effect of oral and transdermal therapy was mostly neutral in hypertensive women. Progestin formulations differed in BP effects among studies, but micronized progesterone, dydrogesterone, and DRSP seemed to have beneficial outcomes. However, the abovementioned assessments are to be interpreted with caution in view of the characteristics of the studies currently available (namely, low number of relevant studies, small sample size, and associated risk-of-bias limitations).

Results from the ongoing Early versus Late Intervention Trial with Estradiol, a trial whose main aim is to examine the effects of oral 17β-E2 on the progression of early (subclinical) atherosclerosis and cognitive decline in healthy postmenopausal women, are estimated to be released in spring 2014. The Kronos Early Estrogen Prevention Study examined the effects of estrogen (CEE 0.45 mg or transdermal 17β-E2 50 µg/day) each with 200 mg of oral progesterone for 12 days per month, or placebo for 48 months on the development of atherosclerosis in postmenopausal women when HT was initiated within 3 years of the menopausal transition. No changes in BP, measured as a secondary outcome were observed in the oral CEE or transdermal E2 arms.

Societies and medical organizations restrict recommendations for the use of HT for the treatment of vasomotor symptoms of menopause and recommend against the use of HT for the prevention of chronic conditions, including coronary artery disease and stroke. Despite the potential effects of HT on BP and the controversial results reported, many guidelines do not include specific recommendations concerning the use of HT in women with hypertension or the clinical follow-up of BP in women initiating HT. The American College of Obstetricians and Gynecologists underscores that several variables may alter the BP effects of HT and estrogen therapy, including the choice of progestin, and state that, in contrast to the vasoconstrictive effect of MPA, natural progesterone has been shown to have either a neutral or a slightly salutary effect on BP. The Royal Australian and New Zealand College of Obstetricians and Gynecologists recommended avoidance or discontinuation of HT in women with uncontrolled hypertension. The recently published Eighth Joint National Committee did not address the effect of HT on BP or the effect of menopause on BP.

There are some limitations to our review. It does not represent a systematic review, and the search started in 2000. However, the search was quite extensive and was updated to November 2013, and its methodology is similar to that of systematic reviews as detailed in Appendix I (Supplemental Digital Content 1, http://links.lww.com/MENO/A107), albeit limited to one major database, namely, MEDLINE. Major trials before 2000 were also included. In comparison with previous reviews, advantages include the fact that it covers pathophysiologic and clinical studies, covers both HT and SERMs, and addresses relevant parameters to help assess the strength of the data available and to achieve confidence in the conclusions derived. Namely, it identifies whether BP was specified as a primary outcome, systematically assesses the risk of bias in each study using an accepted tool, separates large from small trials, and allows the identification of knowledge gap and research needs.

The body of evidence today, including RCTs, does not support a deleterious effect of HT on BP, either in normotensive or in hypertensive women. Transdermal estrogens and natural progestational agents seem to have a beneficial effect. However, the currently available studies, except for those that studied the impact of oral therapy on normotensive women, have several limitations (outlined previously), including the fact that most large trials did not assess BP as a predefined outcome—a shortcoming that needs to be addressed in future trials. In the interim, decisions regarding the use of HT in postmenopausal women with vasomotor symptoms need to be tailored, taking into account a woman’s individual risk profile and age and the evidence presented herein, with careful monitoring of BP when starting such therapy.

Acknowledgments: We would like to thank Ms Aida Farha (medical information specialist, Saab Medical Library, American University
EFECTS OF HORMONE THERAPY ON BLOOD PRESSURE

REFERENCES

ISSA ET AL.


EFFECTS OF HORMONE THERAPY ON BLOOD PRESSURE


